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Medtronic shakes up med-tech with mega-deal to buy Covidien for $42.9B

By Amanda Pedersen, Senior Staff Writer

Medtronic (Minneapolis) shook up the medical technology world on Sunday with news of a mega-sized deal to acquire rival **Covidien** (Dublin, Ireland) for $42.9 billion in cash and stock. The transaction also will allow Medtronic to reincorporate in Ireland, where Covidien is located, thus lowering its tax burden. Interestingly, the deal is contingent on there being no new laws or regulatory actions that would make such inversion deals illegal or prevent Medtronic from capitalizing on Covidien's lower tax rate.

Daily M&A coverage, p. 3

Following a spate of other deals where companies like

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NEWCO ON THE GO

G-Tech Medical's wireless patch gives new meaning to the term gut check

By Omar Ford, Staff Writer

Measuring the behavior of the GI tract to pinpoint disorders can be a difficult task for physicians. While there are numerous tests that physicians can apply during a routine visit, many of these tests are unable to actually capture measurements while the GI system is at work.

G-Tech Medical (Palo Alto, California) has a remedy for this and has developed a wireless, wearable "ECG for the gut" that senses muscle activity from the GI tract over several days and relays data to a smartphone and on to a cloud server. The company said that the data will transform physicians' ability to

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ASIA IN THE SPOTLIGHT

MicroPort Scientific's orthopedics business is expanding in Tennessee

By Kristine Yang, Staff Writer

A Chinese medical device maker has unveiled ambitious plans to expand its presence in the U.S. and create new jobs in the process.

On June 10, **MicroPort Orthopedics** (MPO), a subsidiary of leading Chinese device maker **MicroPort Scientific** (Shanghai), reported it would expand its headquarters in Arlington, Tennessee. The company will renovate the facility and invest $100 million over the next five years in product design, manufacturing capability and to vastly upgrade training and education. MicroPort will fund much of the investment but the Tennessee

See MicroPort, page 8

HTAI 2014

Conway says get in touch early on substantial clinical improvement

By Mark McCarty, Washington Editor

WASHINGTON — A routine sticking point between the Centers for Medicare & Medicaid Services (CMS) and device makers is the new technology add-on payment, a program that relies on demonstrations that a device or diagnostic offers "substantial clinical improvement." Patrick Conway, the chief medical officer at CMS, said in a public forum the agency has talked about this with industry, adding, "these conversations have often gone quite well." However, he urged device makers to contact the agency "earlier rather than later" about the clinical improvement question when eyeing a new tech add-on payment.

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INSIDE

AGREEMENTS/CONTRACTS

Quest begins offering access to Sequenom's MaterniT21PLUS

Staff Report

Sequenom (San Diego), a life sciences company focusing on genetic analysis solutions, and **Quest Diagnostics** (Madison, New Jersey), a provider of diagnostic information services, reported an agreement under which Quest will offer national access to Sequenom Laboratories' MaterniT21 PLUS laboratory-developed test (LDT). Using a maternal blood sample, the noninvasive prenatal test (NIPT) analyzes chromosomal material in cell-free fetal DNA of pregnant women at increased risk for fetal chromosomal abnormalities. Quest expects to begin offering access to the test in the third quarter.

In addition, Quest has formed a license agreement with Sequenom for certain NIPT patents and patent applications. The license agreement is the first formed by Sequenom with a commercial lab in the United States. Quest intends to use the intellectual property for the purposes of developing and validating its own proprietary lab-developed NIPT test. Quest expects to introduce this new offering in 2015. Additional terms of the agreement were not disclosed.

"Noninvasive prenatal testing is one of the most promising new areas of medicine because it delivers highly actionable insights for empowering critical health decisions," said Charles Strom, senior medical director, genetics, Quest Diagnostics. "The MaterniT21 PLUS test stands out for its technological sophistication and clinical usefulness, and is the most well validated to date of the NIPT offerings. Offering access to this test strongly aligns with our strategy to deliver guideline-backed testing services based on the most advanced technologies in order to improve healthcare for patients."

Sequenom has developed a range of laboratory tests, with a focus on prenatal and ophthalmological diseases and conditions.

In other agreements/contracts news, **Natera** (San Carlos, California), a maker of non-invasive genetic testing, and the **Feinstein Institute for Medical Research** (Manhasset, New York) have entered into a research agreement to analyze cell-free circulating tumor DNA (ctDNA) for advanced detection, diagnosis and monitoring of cancer. Under the terms of the

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Coming Wednesday in *MDD Highlights*

THE NON-CLINICAL HAZARDS OF LOW-DOSE CT

The behind-the-scenes story of Medicare coverage of low-dose CT (LDCT) screening for lung cancer is not the kind that makes page A1 in the major daily newspapers, but maybe it should. Physicians and device makers have lobbied extensively on the issue, as is their right, but is getting Congress to weigh in on this issue is really a smart move? To read more, see tomorrow's edition of *MDD Highlights*, an op-ed e-zine that provides fresh commentary from the *MDD Perspectives* blog, http://mdd.blogs.medicaldevicedaily.com. Plus, you'll have access to free articles from *Medical Device Daily*. If you don't already receive this complimentary e-zine, go to medicaldevicedaily.com to opt in.

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DAILY M&A

Novacyt completes its previously reported acqusition of Lab21

Staff Report

Novacyt (Paris), a diagnostics manufacturer that develops solutions in liquid-based cytology for the detection of cancer, including cervical cancer and other non-gynaecological cancers, and **Lab21** (Cambridge, UK), a global specialist in personalized medicine and clinical diagnostics, have completed their stock for stock transaction reported in May.

The transaction was approved by the Novacyt shareholders at an extraordinary general meeting last week. Lab21 is now a 100% subsidiary of Novacyt.

Both companies received significant shareholder support to the transaction and raised a combined €1.5 million from existing shareholders to provide initial working capital to the business. The immediate focus will be to integrate the two businesses at an operational and commercial level and prepare the business for growth. The new company is focused on launching Novaprep in a number of key countries, including China.

The company will also strengthen its board structure and has commenced a search to hire an industry and public market experienced chairman as the company develops its plans for growth and considers its options to raise further development capital.

"We are delighted the transaction has completed swiftly and with such solid support from both sets of shareholders," said Graham Mullis, CEO of the combined company. "We look forward to integrating the two businesses and accelerating our commercialization program which will be heavily focused on the Novaprep platform. A new commercial strategy focused on the Novaprep technology involving investment in marketing, a direct sales channel as well as an expanded international distributor network will be launched towards the end of this year."

The combined group will create an emerging diagnostics products leader with a portfolio of cancer and infectious diseases diagnostic products. It will benefit from significant complementary strengths with Novacyt's R&D capacities and the commercial infrastructure, manufacturing and extensive network of collaboration partnerships of Lab 21.

Immediate revenues will come through the sale of the proprietary screening platform developed by Novacyt, NovaPrep and the existing Lab21 oncology and infectious disease business. Future revenues will come through the increased distribution of NovaPrep and a number of new products developed by the combined group.

Within the combined business, significant operational synergies are expected involving manufacturing, distribution and R&D. Lab21 will manufacture some of the consumables for NovaPrep bringing a major revenue source for the Novacyt technology in-house, control of its supply chain and therefore driving significant gross margin improvements.

Under the terms of the transaction 2,523,058 Novacyt shares will be issued to Lab21 shareholders at an exchange ratio of 0.925 Novacyt share for one Lab 21 share, as remuneration of the Lab 21 shares contribution in kind. 54% of Novacyt fully diluted share capital will be held by Novacyt's shareholders and 46% by the Lab21 shareholders.

Michel Dyens & Co, an investment banking firm based in New York and Paris acted as exclusive financial adviser to Novacyt.

Linklaters LLP acted as legal advisor to Novacyt and Pitmans LLP as legal advisor to Lab21.

In other M&A activity:

• Middle markeet private equity firm **Genstar Capital** reported the signing of a definitive agreement to sell **Evolution1** (Fargo, North Dakota), a provider of consumer directed health (CDH) payments and technology, to **WEX** (South Portland, Maine)for $532.5 million.

Evolution1 provides software, payment and mobile solutions that administer and manage consumer directed healthcare accounts. The company's administrative software solutions, driven by patented technology, allow more than 10 million consumers to spend electronically through prepaid funds in CDH accounts such as health spending accounts (HSAs), flexible spending accounts (FSAs), defined contribution, and more. Evolution1's cloud-based solutions provide a single end-to-end intuitive user experience.

WEX represents more than 7.8 million cardholders and offers payment security and control across a wide spectrum of business sectors. WEX has an additional 10 offices in the U.S. and abroad. The company employs 1,400 associates.

The transaction is expected to be completed in 3Q14 and is subject to customary regulatory approvals. Deutsche Bank and William Blair & Co. acted as financial advisors to Evolution1 and Weil, Gotshal & Manges acted as legal advisor.

• **U.S. HealthWorks** (Los Angeles), an operator of occupational healthcare and urgent care centers, reported it has acquired **California Occupational Clinic of Los Angeles**.

The new Los Angeles location gives U.S. HealthWorks 70 centers and worksites in California, and 212 centers and worksites in 19 states. U.S. HealthWorks already has a Los Angeles center.

Terms of the transaction were not disclosed.

The facility will continue to offer a wide range of occupational healthcare and urgent care services, including diagnosis and treatment for injury and illness, preventive services, pre-employment and post-offer exams and screening, and return-to-work rehabilitative care. //

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HIT BITS

Telcare integrates JDC's messaging into diabetes management solution

Staff Report

Telcare (Bethesda, Maryland) reported that it has integrated **Joslin Diabetes Center** (Boston) approved messaging into its diabetes management solution. The Joslin Diabetes Center's clinical team has worked with Telcare to ensure that its standard message libraries provide diabetes management guidance that is accurate and helpful. This messaging is designed to improve patients' self-management behavior and to encourage patients to actively participate in their diabetes care.

Messaging is a key component of Telcare's diabetes management system. Telcare's system starts with a cellular-enabled blood glucose meter that transmits glucose values instantaneously to a secure server where patients and their doctors can access the information. Messages that provide guidance and coaching are simultaneously displayed on the Telcare BGM and on the secure Internet patient portal.

In other HIT news:

• Eyebridge, a mobile app from **EyeBridge Limited** (London), will provide 24/7 on-demand remote visual assistance for people who are blind or otherwise visually impaired. Within thirty seconds of opening the Eyebridge app, a live operator connects to the customer and his or her smartphone's rear-facing camera, ready to provide video assistance with everything from navigation and product identification to written word interpretation or device operation.

The Eyebridge app in development will be available on both Android and iOS platforms and connect via Wi-Fi and mobile networks.

• **WebMD Health** (New York) launched WebMD Healthy Target, a health improvement program that uses biometric device data from activity trackers, wireless scales and glucose meters to deliver tailored, physician-reviewed, contextually relevant content and motivational tips to individuals looking to develop sustainable health-conscious habits. WebMD Healthy Target will provide valuable assistance to individuals looking to manage chronic conditions like Type 2 diabetes and obesity, as well as to a broader audience interested in achieving their fitness goals or more generally living a healthier lifestyle.

Available within WebMD's flagship mobile app for iPhone, Healthy Target can translate step, sleep, weight and blood glucose data from multiple well-known device manufacturers, including Entra, Fitbit, UP by Jawbone and Withings, into actionable insights. In addition, iPhone 5s users have the option to track their steps with their smartphone. Users can manually input their biometric data into Healthy Target or connect their devices. //

Agreements

Continued from page 2

agreement, Natera will provide funding to the Feinstein Institute, which will contribute blood and tissue samples to Natera for the development of technology that can detect tiny fragments of tumor DNA in a patient's bloodstream.

Circulating tumor DNA (ctDNA) are small pieces of mutated DNA that tumor cells release into the bloodstream. Analyzing ctDNA in the bloodstream may decrease the need for traditional biopsies, which involve extracting a small piece of tissue from the body for examination, and which, in addition to being invasive, often do not give a comprehensive genetic view of the full tumor.

"Earlier cancer detection leads to better clinical outcomes," said Peter Gregersen, director of the Feinstein Institute's Center for Genomics and Human Genetics. "The Feinstein Institute is delighted to partner with Natera for the development of cutting-edge diagnostic methods, and we are optimistic about the application of Natera's core technology to address the unique challenges in early cancer detection and monitoring."

Natera specializes in designing targeted assays that use single nucleotide polymorphisms and unique statistical algorithms to analyze cell-free DNA for the presence of abnormalities. Analyzing cell-free DNA from a fetus during pregnancy is technically similar to analyzing cell-free DNA from a tumor, since the unique DNA of each are mixed in low concentrations with the DNA of the host. These genetic tests can be performed non-invasively, through a simple blood draw. Natera's tests have demonstrated accurate and reliable clinical performance in more than a dozen peer-reviewed scientific and clinical publications, the company said.

The Feinstein Institute for Medical Research is a biomedical research institute. //

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FINANCINGS

PowerVision completes $30 million Series D round to fund more studies

Staff Report

PowerVision (Belmont, California), a device company developing a fluid-based accommodating intraocular lens, reported that the company has completed a $30 million Series D financing round. New investors Aisling Capital and Correlation Venture Partners as well as existing investor Venrock added $10 million to the $20 million closing earlier this year from PowerVision's existing investors.

Proceeds of the funding will be used to complete patient enrollment in the ongoing CE mark study of the FluidVision accommodating intraocular lens, with patient enrollment expected to be completed by the end of the year, and receipt of the CE mark and the subsequent launch of the U.S. pivotal study coming in 2015.

The FluidVision lens is designed to permanently restore clear vision at all distances for patients with cataracts and presbyopia.

"Based on data reported to date, we believe that the FluidVision lens could become the first truly accommodating intraocular lens to hit the market and become a new standard of care for cataracts and presbyopia surgery," said Barry Cheskin, president/CEO and co-founder of PowerVision. "Current treatment methods fall short, and most patients must still rely on reading glasses or other corrective lenses to see both near and far. The FluidVision lens would eliminate that need, and could provide a new option for millions of people with these conditions."

Data from the company's pilot study, which were presented at the **American Society of Cataract and Refractive Surgery** (ASCRS) Annual Symposium in April, showed that patients who received the FluidVision lens in one eye as part of cataract surgery had excellent distance vision, averaging better than 20/20 at six-month follow-up. Visual acuities at intermediate and near were also impressive at six months, approximately 20/25 and 20/33 respectively, when tested in one eye, and allowed patients to read without glasses. The visual outcomes provided by the lens should improve even more in patients when they have lenses implanted in both eyes. The study also confirmed the safety of the lens, with no clinical complications or adverse events reported.

"We remain on track to complete patient enrollment for our CE mark study by the end of the year. This funding will support those efforts and should allow us to get the CE mark in 2015 and launch our pivotal study in the U.S. in early 2015," Cheskin said in a statement.

PowerVision's major investors now include Aisling Capital, Correlation Ventures, Advanced Technology Ventures, Frazier Healthcare, Venrock, Johnson & Johnson Development Corporation and Medtronic. //

GRANTS

Inscopix launches $1M DECODE in call to action for BRAIN Initiative

Staff Report

Inscopix (Palo Alto, California) reported the launch of its Deciphering Circuit Basis of Disease (DECODE) grant program in response to President Obama's "all hands on deck" call to action for the BRAIN Initiative. Through the $1 million DECODE grant program, Inscopix said it wants to bolster extramural research efforts for investigating how aberrant neural circuit activity contributes to brain malfunction in a diverse range of neurological and psychiatric disorders.

Inscopix's DECODE competitive grant application process will be open to principal investigators or group leaders at any public or private research organization. A panel of neuroscientists and brain-disease experts will select between three and five meritorious proposals that will receive the two-year in-kind award comprising Inscopix's nVista HD imaging systems, and access to its robust scientific and intellectual infrastructure. Through this grant, Inscopix aims to identify and support neuroscience researchers who push the envelope, foster new avenues of thought, and shift paradigms in how brain dysfunctions are studied and treated. //

PEOPLE IN PLACES

• **Cryoport** (Lake Forest, California), a provider of cryogenic logistics solutions, has named Ramkumar Mandalam to its board. Additionally, he has been appointed to serve as a member of the compensation and nominating and governance committees. Mandalam joins Cryoport's board with twenty years of experience in the development of biologics. He is currently the president/CEO of Cellerant Therapeutics. Cryoport provides cryogenic logistics solutions to the life sciences industry through the combination of purpose-built proprietary packaging, advanced information technology and logistics expertise, which manages the entire cold chain logistics process.

• **Genstar Capital** (San Francisco) has named Harry Totonis to the firm's strategic advisory board. Totonis most recently was president/CEO of Surescripts. Genstar Capital is a middle market private equity firm that focuses on investments in targeted segments of healthcare, software, financial services, and industrial technology industries.

• **KEW Group** (Cambridge, Massachusetts) has named Scott Schell president/CEO. Schell, who will also become a member of KEW's board, will commence his position at the company effective July 1. Most recently, Schell was instrumental in assisting the Cleveland Clinic in developing its strategy for population health management. KEW is focused on cancer care by empowering oncologists to access and apply genomic insights to design individualized treatment approaches for patients.

Medtronic

Continued from page 1

Medtronic have sought to escape the U.S. tax regime by merging with a foreign company, Sen. Carl Levin (D-Michigan), introduced a bill last month to close the loophole. The legislation, co-sponsored by 14 senate democrats, would also require that the foreign target's shareholders own at least half of the combined company, rather than the current 20% threshold.

While some industry watchdogs did point out several "pros" associated with the proposed Medtronic-Covidien deal, not everybody in the industry sees this acquisition in a favorable light.

Larry Haimovitch, president of **Haimovitch Medical Technology Consultants** (Mill Valley, California) and a regular contributor to *MDD*, said his initial reaction to the news was "OMG."

"I was absolutely stunned," Haimovitch said. "Then I went from stunned to bummed. Bummed because I really think this is very bad for a lot of our small med-tech world."

He pointed out that not only would the deal take out Covidien, which has been a very active buyer in the industry, much more so than Medtronic in recent years, but it will make it increasingly difficult for smaller companies to compete with mammoth corporations in the industry.

As for the tax issue, Haimovitch said it is "really unfortunate" to see taxes moving the needle so much. "So the tax tail is wagging the dog here and that is not a good thing," he said.

But the senate bill introduced to close the loophole might not be the best solution. Rather than trying to stop deals like the proposed Medtronic-Covidien merger, U.S. policy makers should consider fixing the root of the problem, the tax laws. Otherwise, he said, "it's like putting wallpaper on a building that's falling down."

Larry Biegelsen, senior analyst for Wells Fargo Securities, covering medical supplies and devices, said in a research note that the deal could trigger further consolidation in the industry. He said that Medtronic could potentially go after other M&A opportunities, particularly in the U.S., because the Covidien acquisition will provide increased access to cash and additional segments.

"We believe Covidien represents the best inversion opportunity for Medtronic," Biegelsen said. Pointing to all the same strategic fits that Medtronic noted, he added that Medtronic focused on Covidien's strength in peripheral vascular, neurovascular and advanced energy as highly complementary to Medtronic's portfolio.

The proposed transaction is valued at $93.22 per Covidien share, based on Medtronic's closing stock price of $60.79 a share last Friday. According to Medtronic, once the deal is completed, the company will have significantly advanced its position as a medical technology and services company.

As a direct benefit of the company's new financial structure, Medtronic said it will commit to $10 billion in technology investments over the next 10 years in areas such as early stage VC investments, acquisitions and R&D in the U.S., above and beyond Medtronic's and Covidien's existing plans.

"The medical technology industry is critical to the U.S. economy, and we will continue to invest and innovate and create well-paying jobs," said Medtronic CEO Omar Ishrak in a company statment. "Medtronic has consistently been the leading innovator and investor in U.S. med tech, and this combination will allow us to accelerate those investments. These investments ultimately produce new therapy and treatment options that improve or save lives for millions of people around the world."

Ishrak also noted that although the company intends to relocate in Ireland, it will continue to have its operational headquarters in Minneapolis.

"This acquisition will allow Medtronic to reach more patients, in more ways and in more places. Our expertise and portfolio of services will allow us to serve our customers more efficiently and better address the demands of the current healthcare marketplace," Ishrak said.

"Covidien and Medtronic, when combined, will provide patients, physicians and hospitals with a compelling portfolio of offerings that will help improve care and surgical performance," said José Almeida, chairman, president, and CEO of Covidien. "This transaction provides our shareholders with immediate value and the opportunity to participate in the significant upside potential of the combined organization."

The per-share consideration represents a premium of 29% to Covidien's closing stock price on Friday, the last trading day prior to the announcement.

The transaction is expected to be accretive to Medtronic's cash earnings in fiscal year 2016, the first full fiscal year, and significantly accretive thereafter. The transaction is also expected to be accretive to GAAP earnings by fiscal year 2018.

Medtronic also said the combination of it and Covidien is expected to result in at least $850 million of annual pre-tax cost synergies by the end of fiscal year 2018.

Paul Teitelbaum, managing director and medical device/healthcare IT M&A expert at Mesirow Financial's Investment Banking Group, had a more optimistic view on what this merger means for the industry. The deal is the latest example of the industry's "frenzy of M&A activity since the beginning of the year and since late 2013," Teitelbaum told *Medical Device Daily*.

"It's an interesting merger in the sense that it diversifies Medtronic very significantly in terms of where it's been," Teitelbaum said. For example, he said it expands Medtronic into areas like patient monitoring and other services, beyond implantable devices.

The deal will also expand Medtronic's revenues outside the U.S., Teitelbaum said, giving the company more of a presence in Asia countries besides China and Japan. "Diversification is something important to [Ishrak]," Teitelbaum said.

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G-Tech

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determine underlying causes of functional GI disorders and the effectiveness of treatments.

"The idea is that people wear these patches for a few days," Steve Axelrod, president/CEO of G-Tech, told *Medical Device Daily*. "They're thin and light, comfortable and conforming, you can go about your daily life. That's very important for a GI diagnostic. When you're not doing normal things your GI system doesn't behave normally. If you go to the doctor and have a test done, your GI system shuts down."

G-Tech's device uses traditional wired ECG style hardware, essentially 3 ECG systems in parallel, with 30 electrodes in a grid across the abdomen. The company digitizes and records raw data from each of the 18 sense electrodes for later analysis by a custom LabVIEW-based application. G-Tech has developed algorithms that identify the instances of rhythmic electrical activity associated with mixing and propulsion of the luminal contents of the stomach, small intestine and colon.

Data algorithms will create each person's unique internal GI signature based on their responses to specific meals, medications and patterns leading to and during symptoms (pain, cramps, nausea, bloating).

Axelrod said that the patches could lead to greater insight regarding patients than standard measurements being used today.

"You can't do a 20 minute measurement and learn very much about the GI system because it's a 24-hour cycle," he said. "We call it an ECG for the gut. When you measure the heart with an ECG for one second you've got a heartbeat, in 10 seconds you have some pretty decent data. Our target is a patch that will last for three days. The doctors will put the patches on you and say we're going to learn about the function of your GI system. Physicians using the system should be able to give you a profile of the performance of your digestive system. The physicians can go from there and target the therapies that work best for you."

FDA approval could be a little more than two years away for the device.

"I have a 650 task-project-plan that gets us to product release in 38 months," he told *MDD*. "We'll do a clinical trial with the second prototype. That's the version before the final manufacturing prototype. With the second prototype we'll do maybe a thousand person clinical trial and with that, we'll collect the data that we need for the FDA and to show insurance companies that this works and is going to be cost effective and save money."

The firm said that clearance could should be pretty standard since the device wasn't making a diagnosis of the disease.

"We believe that FDA clearance should be pretty straightforward," he said. "This is a patch that you wear on your body. It's strictly non-invasive and we're going to let the doctors do the actual diagnosis. We will present them with data, on how active a person's stomach, small intestine or colon is . . . and let them be the ones to make judgment on the diagnosis. That will make the FDA pathway for us much easier."

G-Tech was one of several companies to recently receive funding from **Breakout Labs** (San Francisco), a nonprofit fund that supports scientific innovation. *Medical Device Daily* reported on **EpiBone** (New York), another company that garnered funding from Breakout Labs in Monday's issue (*Medical Device Daily*, June 16, 2014). Breakout Labs also provided funding for Cortexyme, a firm developing therapeutics that could alter the course of Alzheimer's and other disorders of aging. //

PRODUCTS

• **Edwards Lifesciences** (Irvine, California), a maker of heart valves and hemodynamic monitoring, has received FDA approval for its Edwards Sapien XT transcatheter aortic heart valve for the treatment of high-risk and inoperable patients suffering from severe symptomatic aortic stenosis. This system includes the 29mm valve size for patients with a large native annulus. The Sapien XT valve will be available to patients at cardiovascular centers, along with the NovaFlex+ transfemoral delivery system that can be delivered through a low-profile 16-French expandable sheath and the Ascendra+ transapical and transaortic delivery systems. "There is a substantial and growing body of evidence that the SAPIEN XT valve benefits both high-risk and inoperable patients, and clinicians have documented these consistently positive results in both randomized studies and European country registries," said Martin Leon, director, Center for Interventional Vascular Therapy at **NewYork-Presbyterian/ Columbia University Medical Center** and professor of medicine at the Columbia University College of Physicians and Surgeons. Leon was the co-principal investigator for the PARTNER II Trial, which was Edwards' second randomized controlled trial of a transcatheter valve and evaluated the SAPIEN XT valve.

• **SpinalCyte** (Houston) a spinal technology company focused on autologous regrowth of the spinal disc nucleus using human dermal fibroblasts, reported an agreement between SpinalCyte and Howard An, a professor of orthopedic surgery and director, division of spine surgery and spine fellowship program, **Rush University Medical Center** (Chicago), to complete the final animal trials. The initial animal trials, using 16 rabbits, succeeded in regrowing the nucleus of the spinal disc and restoring disc height by over 80%. The final animal trial is scheduled to last 10 months and will increase the number of rabbits used to 64. It will also increase the *in vivo* monitoring by eight weeks. "I am encouraged by our previous work with this technology and look forward to further scientific data to prove this technology as a future treatment for degenerative disc disease," said An. The nucleus pulposus is a gelatinous material that acts as a cushion or shock absorber to the spinal column. It functions to distribute hydraulic pressure in all directions within each disc under compressive loads. The nucleus pulposus consists of chondrocytes, collagenfibrils, and proteoglycan aggrecans.

Microport

Continued from page 1

government will also provide a grant to support the expansion, said Jonathan Chen, senior VP of international operations and investor relations from MicroPort. But the total amount of the Tennessee grant was not disclosed.

The announcement follows a fundraising push in May through which Microport Scientific raised $100 million by issuing convertible bonds to Singapore's sovereign wealth fund GIC. The company said it would use the funds to pay back a loan from Japan's **Otsuka Medical Device** (Tokyo), which holds a 33% stake in Microport. (*Medical Device Daily*, June 16, 2014)

MicroPort entered the orthopedics arena in June 2013 by acquiring the OrthoRecon business from **Wright Medical** (Arlington, Tennessee). The acquisition, valued at $290 million, was also the biggest by a Chinese company in the U.S when it was completed in the first quarter of 2014. The OrthoRecon business includes hip and knee implant products. The business generated global revenue of $269 million in 2012.

After the acquisition, MicroPort Orthopedics became the largest division under the MicroPort Scientific Group and the sixth largest supplier of orthopedic products, covering more than 60 countries. It is separate from MicroPort's drug-eluting stent business in China.

MPO is the global headquarters for MicroPort's entire orthopedic business. Such expansion will push the development in the Chinese market as well.

"In particular, we will be able to invite Chinese surgeons to train with U.S. surgeons at our world-class medical education facility in Memphis that will be constructed with these funds. In addition to our local Shanghai training centers, this will be another opportunity for Chinese surgeons to get access to best available training from Western world," said Chen.

"We can support China orthopedic surgeons with FDA approved manufactured product, medical education, product development, and clinical data support. All these activities are centralized in Memphis."

Since the acquisition was completed in January, the company has hired 97 people and it plans to create another 170 jobs. The new expansion will primarily focus on the training facility.

"The team at MicroPort Orthopedics is excited to partner with the state of Tennessee to expand our operations," said Ted Davis, CEO of MicroPort Orthopedics in an announcement. "Together, MicroPort and Tennessee will create high-quality jobs, attract and retain top caliber employees, and manufacture world-class medical devices for the global orthopedic market."

Davis said local and state officials had been generally supportive of the expansion, in particular the Department of Economic and Community Development.

The support will allow MicroPort to speed up plans to build a state-of-the-art training facility to educate new surgeon customers and sales teams, Davis said, adding that the company looked forward to strengthening ties with the city of Arlington and the state of Tennessee.

The state exports over $32.4 billion worth of products, medical equipment and supplies being the top category, noted Bill Hagerty, Economic and Community Development Commissioner of Tennessee.

"Our state's strength in research and development allows global companies like MicroPort Orthopedics to feel confident in their continued investment, knowing their commitment to innovation is valued and supported in Tennessee," Hagerty said.

Governor Bill Haslam, for his part, thanked MicroPort for its continued investment in Tennessee and the jobs it was creating.

"Expanding companies already located here is one of our priorities, and this announcement supports our goal of becoming the number one location in the Southeast for high quality jobs."

Founded just 15 years ago, Shanghai-based MicroPort is already one of the leading device providers in China.

The company has just formed a joint venture with the **Sorin Group** in China to develop and market cardiac rhythm management devices. (*MDD*, Jan. 14, 2014).

MicroPort reported turnover of ¥938 million ($150 million) and gross profit of ¥760 million ($122 million) in 2013. By the end of 2013, it had filed 584 patents, including 409 Chinese patents, 102 under the patent cooperation treaty and 79 international patents.

Chinese companies have been actively seeking investment opportunities in the U.S. and Europe. In the first quarter of 2014, Chinese investors announced high-tech deals worth more than $6 billion in the U.S. And from 2000 to 2013, there were 17 deals in healthcare and medical device sectors with a total value of $491 million, according to a recent report by Rhodium Group, a U.S. consultant.

Chinese firms hired more than 70,000 Americans in 2012, compared with a mere 10,000 in 2007, according to Rhodium.

Wright Medical moved out from the Arlington facilities to its headquarters also in Tennessee after the acquisition. Wright's shares saw a lift after it quit the OrthoRecon business. //

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HTAI

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Conway offered his remarks at the annual meeting of **Health Technology Assessment International** (HTAi; Edmonton, Canada), and said CMS staffers "can help guide you on the outcomes that will be meaningful" where substantial clinical improvement is concerned. He acknowledged the existence of "different statistical constructs for FDA and CMS" on whether a device offers a meaningful difference from the standard of care. However, Conway said CMS is "working with industry on what the various cut points should be" for measuring that improvement.

Conway said life at CMS "is like dog years. Three years feels like 21," he quipped, but he turned serious when addressing recent developments in Medicare spending, which he said have exhibited "the lowest cost growth . . . in the past 50 years." Conway acknowledged the effect of the recession on spending, but said the agency's actuaries believe the recent low spending growth rates can be attributed to "fundamental shifts in our delivery system as well." He said recent Medicare data indicated that all-cause, 30-day readmission rates are at 17.5%, adding that the hospital-acquired condition program at CMS has saved 15,000 lives and prevented 540,000 adverse events. He said these translate into $4 billion in savings.

The agency is working with private payers on changing payment models for primary care physicians (PCPs), Conway said, describing this as akin to a shared savings program for specialists. The program for PCPs emits "a signal that is very strong, and moves them from a fee-for-service [FFS] model and toward a care management model," he explained. Conway also said, "hundreds of providers . . . have elected to move into phase II, the risk-bearing phase" for this program.

Conway said more than 350 accountable care organizations (ACOs) now serve more than five million Medicare beneficiaries, but he remarked that the question for ACO 2.0 is: "How could you move ACOs from shared savings to a population-based model?" He explained that the next round of ACO contracts will tackle outpatient and post-acute care settings, but he said the agency is still working on implementation models for 2.0. "We literally are having quarterly reviews, if not more" to track the progress of this phase, he said.

When it comes to diagnostic testing, Conway said, "we think a lot about individual response." He said for many diseases, "ideally the treatment would be guided" by a diagnostic. The companion diagnostic (CDx) is "a huge and growing area," he said, vowing, "we want to support innovation." He said that the coverage and evidence group (CAG) "is trying to think about how to do this on a national and local level," but he pointed out that CAG "is 35 people – approximately 14 physicians . . . so that creates some challenges."

Conway said while the CAG staffing problem presents "a real challenge in terms of what you can tackle . . . we are willing to engage industry, FDA and others on what is the best approach" in determining coverage. He touted the case of transcatheter aortic valve replacements (TAVR), saying, "we worked with the device maker, providers and FDA," and turned out a coverage decision in six weeks. "That is unheard of in the U.S.," Conway said.

"We have made more CED decisions on average recently," Conway acknowledged, but he said those decisions handled "on a national level are more complex" than CEDs undertaken by Medicare administrative contractors. He returned to the ACO discussion, stating that CMS has heard that "you guys need to think about technology carve-outs" to avoid loss of a device's use under the ACO umbrella. He said CMS is "looking at this so we don't limit the use of technology" unnecessarily in ACOs.

Evidence for robotic CABG iffy

Anna Maria Buehler of **Hospital Alemão Oswaldo Cruz** (São Paulo, Brazil), was among the presenters in a session of technology evaluations at HTAi 2014, reviewing the data for robotically-assisted coronary artery bypass grafting. Buehler said she had "contacted the robotic system manufacturer, which did not provide any additional information," in reference to **Intuitive Surgical** (Sunnyvale, California), maker of the da Vinci system. Buehler said she located 563 citations in the literature, but that "only three met our criteria" for the final review. All three, Poston, Bachinsky and Sutter, were non-randomized studies. Poston and Bachinsky were hybrid procedure trials, Buehler observed, although she said "the patients were similar with regard to age, gender and BMI" in each. She said Sutter lacked some comorbidity data, such as diabetes status, adding that while Bachinsky suffered from a high risk of selection bias, "all the trials had at least one domain of unclear or high risk" for bias.

Buehler said the amount of time in surgery varied across the trials, offering low quality evidence on this point, which also applied to time in ICU and overall length of stay. However, "the quality of evidence started out at low because the trials were not randomized," Buehler remarked.

For atrial fibrillation and infarct, the quality of evidence was again low, Buehler said, adding that for stroke, she saw a "very wide confidence interval, with few events," a state of affairs that also applied to all-cause mortality.

Robotic CABG "was more time consuming [and] reduced both ICU and hospital length of stay" in the three trials, but no difference in all-cause mortality emerged, Buehler said. She noted that the data suggested robotic CABG could tamp down on mortality associated with afib, and she said the procedure seems feasible despite a steep operator learning curve.

Still, Buehler said, there was "not adequate evidence showing that robotic assisted CABG is better than traditional procedures," concluding her presentation with the remark, "we need randomized clinical trials to determine the long-term benefits." //

Medtronic

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Teitelbaum said he attended a conference in San Francisco last week where Medtronic's Stephen Oesterle, senior VP for medicine and technology, was a key speaker. Interestingly, according to Teitelbaum, Oesterle said that Apple and Google will soon be Medtronic's biggest competitors because those companies are rapidly moving into the healthcare space with mobile apps and remote health monitoring solutions.

"Those are gigantic companies with virtually limitless imagination and passion . . . look at how powerful and how successful they have been in getting into the hands of just about every doctor in the world," Teitelbaum said. "Who knows what [Apple and Google] are going to do in healthcare and that's why [Oesterle] sees those two companies being big competition."

Given that context, Teitelbaum said it is not surprising that Medtronic is being such an aggressive buyer this year, particularly of companies in remote monitoring and healthcare IT, like **Cardiocom** (Chanhassen, Minnesota).

Glenn Novarro, an analyst with RBC Capital Markets, said in a research note that while the sector will move higher on the prospects of further M&A, recent large deals in the industry suggest that larger-cap companies are now thinking about bigger deals, and not tuck-ins. "In our opinion, this means small-cap med-tech companies in cardio, spine, and extremities may no longer be targets over the near to intermediate term," Novarro said.

Medtronic also said that merging with Covidien will accelerate its three fundamental strategies: therapy innovation; globalization; and economic value. The companies noted that they have combined revenues of $13 billion from outside the U.S., of which $3.7 billion comes from emerging markets. With Covidien, Medtronic said it will be able to provide a broader array of complementary therapies and solutions that can be packaged to drive more value and efficiency in healthcare systems. Both companies' deep relationships with healthcare system stakeholders will provide enormous ability to identify and create further value-based solutions.

Medtronic's financial advisor is Perella Weinberg Partners and its legal advisors are Cleary Gottlieb Steen & Hamilton and A & L Goodbody. Covidien's financial advisor is Goldman Sachs & Co. and its legal advisors are Wachtell, Lipton, Rosen & Katz and Arthur Cox. Bank of America Merrill Lynch provided committed financing for the transaction.

L.E.K. Consulting (Boston) experts noted in an e-mail to *Medical Device Daily* that the proposed merger carries benefits. According to the firm, the Medtronic-Covidien deal increases scale and relevance in the face of hospital and payer consolidation, particularly in the U.S. Also, the firm said, outside the U.S. it provides more scale and relevance in geographies where each company has established infrastructure which it can now leverage with a broader portfolio of products.

"Through this merger, we will continue to see the emergence of different business models, especially ones that entrench in specifically focused disease areas and go more 'vertical including services' and others that will play a relevance game with proximity to customers," L.E.K. Consulting said. "For smaller medical device companies, it means that fewer large companies are going to have entrenched positions within the market-access and proximity to customers, that means that small companies with innovation will increasingly consider large partners like Medtronic for development and commercial access."

Leerink (Boston) analysts Danielle Antalffy and Richard Newitter also issued a research note regarding the deal. "With minimal overlap across product lines, Covidien provides meaningful scale and incremental breadth to Medtronic, which now will have product offerings touching nearly all areas of the hospital," Antalffy and Newitter said. "Covidien brings a steady, mid-single-digit sales growth heavily weighted towards hospital supplies with some complementary technologies including a $1.2 billion peripheral vascular business, a nearly $1 billion patient monitoring business, and a [roughly] $500 million neurovascular business. This deal overall is a strong signal that scale and portfolio breadth are increasingly being viewed by med-tech industry leaders as paramount to remaining competitive in a post-ACA environment." //

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CARDIOLOGY EXTRA

Keeping you up to date on recent developments in cardiology

By Amanda Pedersen, Senior Staff Writer

Vascular endothelium pegged for control of blood to brain

Establishing the mechanisms responsible for controlling blood flow to the brain has proved difficult, but a recent statement indicates that the puzzle may be coming together. A new study appearing in the online edition of the *Journal of the American Heart Association* describes the work done by researchers at **Columbia Engineering** (CE; New York) identifies a new component of that control mechanism, namely the the vascular endothelium, which is said to play "a critical role in the regulation of blood flow in response to stimulation in the living brain."

The statement points out that the brain increases local blood flow in response to neuronal activity, which is the behavior picked up by functional magnetic resonance imaging (fMRI), and researchers discovered that the vascular endothelium, already known to serve this function in other areas of the body, is a primary agent in bolstering blood flow despite a perception that a "more specialized mechanism" was the primary driver. Much of the research in the field has been focused on the cells surrounding the vessels in the brain, but Elizabeth Hillman, associate professor of biomedical engineering at CE, said, "we think we've found a missing link in our understanding of how the brain dynamically tunes its blood flow to stay in sync with the activity of neurons."

Hillman, who has spent more than a decade evaluating this phenomenon with a variety of imaging tools, remarked, "earlier studies identified small pieces of the puzzle, but we didn't believe they formed a cohesive 'big picture' that unified everybody's observations. Our new finding seems to really connect the dots," she said. The effort to shed light on this mechanism entailed the development of "new ways to both image the brain at very high speeds, and also to selectively alter the ability of endothelial cells to propagate signals within intact vessels," the statement explains.

Hillman and her colleagues used a variety of techniques that employ optics, including a high-speed camera paired with synchronized, strobed LED illumination to pick up chromatic changes, thus rendering a depiction of oxygenation. They also used focused laser light combined with a fluorescent dye in the bloodstream to cause oxidative damage to the inner endothelial layer of blood brain arterioles, while leaving the rest of the vessel intact and responsive. This effort demonstrated that after damaging a small section of a vessel using the laser, the vessel no longer dilated beyond the damaged point.

When the endothelium of a larger number of vessels was targeted in the same way, the overall blood flow response of the brain to stimulation was significantly decreased," the statement noted. Hillman said the new understanding "unifies what is known about blood flow regulation in the rest of the body with how it is regulated in the brain." She asserted, "this has wider reaching implications since there are many disease states known to affect blood flow regulation in the rest of the body that, until now, were not expected to directly affect brain health." One possible application would be delving into how involvement of the endothelium might explain neural deficits in diabetics, but this research could also point the way to new diagnostics tests and treatments for neurological conditions associated with broader cardiovascular problems.

The heartache/heart connection

They say a broken heart can become a damaged heart, and a recent statement explains how this might be true. The statement explains that researchers may have established how stress, emotional shock, or overexertion can trigger heart attacks in those who are susceptible, with hormones released during these events appearing to cause bacterial biofilms on arterial walls "to disperse, allowing plaque deposits to rupture into the bloodstream," the statement indicates.

This research appears in *mBio*, the online open-access journal of the **American Society for Microbiology** (Washington), and David Davies of **Binghamton University** (Binghamton, New York), one of the authors on the study, said the hypothesis "fitted with the observation that heart attack and stroke often occur following an event where elevated levels of catecholamine hormones are released into the blood and tissues, such as occurs during sudden emotional shock or stress, sudden exertion or over-exertion."

Davies and his colleagues are said to have isolated and cultured several species of bacteria from diseased carotid arteries they had removed from atherosclerotic patients. They discovered "multiple bacterial species living as biofilms in the walls of every atherosclerotic carotid artery tested," the statement notes. Under ordinary circumstances, these biofilms are resistant to both antibiotic treatment and immune system efforts to clear them out, but a "molecular signal" can trigger dispersion, which releases enzymes that digest the scaffolding that keeps the bacteria pent up in the biofilm. These enzymes are capable of digesting nearby tissues that prevent the rupture of arterial plaque.

Davies claims this behavior could explain "the long-held belief" that stress, exertion and shock can trigger heart attacks. They tested their theory by applying norepinephrine to biofilms formed on the inner walls of silicone tubing. Davies explained that Pseudomonas aeruginosa exhibited a biofilm dispersion response when exposed to norepinephrine.

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CARDIOLOGY EXTRA

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Editing cholesterol out

Medical science is on the cusp of some interesting revolutions, including the possibility of genetic manipulation that might have seemed unimaginable a mere 20 years ago. However, researchers at the **Harvard Stem Cell Institute** (HSCI; Cambridge, Massachusetts) in collaboration with researchers at the **University of Pennsylvania** (Philadelphia) have devised a "genome-editing" approach for permanently taming down cholesterol levels in mice by means of a single injection, an advance that offers the prospect of cutting the risk of heart attacks in humans by up to 90%.

The statement reminds the reader that a group of researchers in France discovered in 2003 that PCSK9 is a cholesterol regulator thanks to their studies of families with high cholesterol levels, describing the impact of mutations in this gene on the incidence of heart attacks. However, the statement notes that the mutations seen in this study "are extremely rare and are limited to a few families." However, researchers in Texas are said to have discovered that about 3% of the population "have mutations in PCSK9 that have the opposite effect," exhibiting low-density lipoprotein (LDL) levels 15%-28% lower than average.

Those equipped with this genetic variant are said to have a risk of heart attack that is between 47% and 88% below average. The magic here is that this knowledge can be paired with a technology called CRISPR/Cas9, first discovered in 2007, the study showed.

Kiran Musunuru of HSCI said Cas9 "is a protein that will create a break in DNA, and the CRISPR is an RNA component that will bind to a matching sequence and directs the Cas9 to that sequence in the DNA in which you are interested." He said the use of the two "creates a break where you want it. The cell can then repair itself, though often with errors, which is useful if you want to disrupt a gene to create a 'knockout' of the gene." Musunuru observed that the first question he and his colleagues had to answer was "whether we could get CRISPR/Cas9 into the liver, and once we got it into the liver, would it function properly?" Fortunately, the combination made it to the rodent liver, and while Musunuru and his colleages wondered whether it would yield the desired effect, "it turned out to have a dramatic effect.

Within three to four days of delivering the system into the liver, the majority of the PCSK9 gene copies in all of the liver cells were disrupted, knocked out. And what we hoped to see was much less of the protein product in the bloodstream, which is what we saw," he said. Musunuru added that the experiment resulted in a reduction of cholesterol levels of 35-40%, which would reduce heart attack risk by up to 90%. Musunuru is said to have emphasized that a decade might pass before this would appear in a phase I trial in humans. The research appears in the online edition of *Circulation Research*.

Air pollution-infarct association murky

Air pollution has long been a suspect in various ailments of the heart, but a recent statement suggests that the link is stronger for some conditions than others, including instances in which the evidence provides little compelling evidence of a link. A team of researchers set out to flesh out the short-term biological impact of air pollution on cardiovascular disease with the use of data from three national collections in the UK and Wales between 2003 and 2009. The three data sets are the Myocardial Ischemia National Audit Project (MINAP), which tracks hospital admissions for heart attack/stroke; the Hospital Episode Statistics (HES) on emergency admissions; and mortality data collected by the UK Office of National Statistics (ONS). The aggregate data set includes more than 400,000 heart attacks, more than two million emergency admissions for cardiovascular problems; and 600,000 deaths chalked up to heart attack/stroke, and these events were linked to average levels of air pollutants over a period of five days using data from the monitoring station nearest to the residence of those whose data appear in these databases. Among the findings is that no clear link exists between any air pollutant and cardiovascular deaths with the exception of PM2.5, which the data suggest is associated with an increased risk of irregular heart rhythms – including atrial fibrillation – and pulmonary embolism. Only nitrogen dioxide "was linked to an increased risk of a hospital admission for cardiovascular problems, including heart failure, and an increased risk of a particular type of heart attack (non-ST elevation) in the MINAP data," the study showed. The findings suggest that "there is no clear evidence implicating short-term exposure to air pollution in boosting the risk of heart attacks and stroke," the statement concluded, although the statement indicateed that the data suggest "a clear link between particulate matter levels and heightened risk of atrial fibrillation and pulmonary embolism."