BioWorld MedTech

Clarivate Analytics

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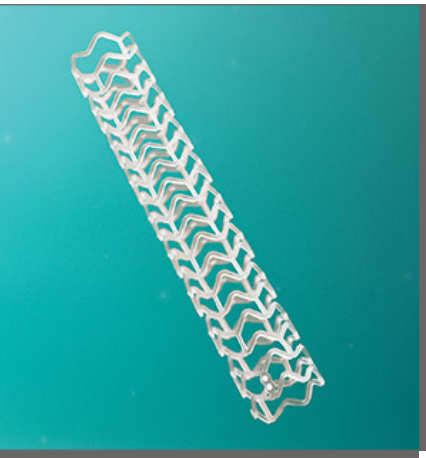
November 1, 2017
Volume 21, No. 212



TCT 2017

Vessel size matters, but strut thickness is the endgame for Abbott's bioabsorbable GT1 stent

By Mark McCarty, Regulatory Editor

DENVER – The story of the bioresorbable coronary artery stent is far from over, but three-year data from the Absorb III study of the Absorb GT1 by Abbott Park, Ill.-based Abbott Vascular suggests that vessel size matters, but isn't everything where scaffold thrombosis is concerned. On the other hand, 30-day data from Absorb IV led the principle investigator to remark that strut thickness is the central issue

See Abbott, page 3

Inside

ANVISA striving for harmonization

With new GMP regulations, Brazil aims to clear backlogs

By Sergio Held, Contributing Writer

BOGOTA, Colombia – The Brazilian med-tech regulator is strengthening inspections linked to good manufacturing practices (GMP) certificates abroad as it works to clear a regulatory backlog and better harmonize its process with other authorities around the world.

ANVISA (for its Portuguese acronym) issued a new regulation, RDC 183/2017, that sets clear requirements for the issuance of GMP certificates in the Latin American country for manufacturers located outside Brazil and outside the Mercosur subregional trade bloc.

See Brazil, page 4

Seeks additional indication

Mercator Medsystems leaps forward with Bullfrog into LIMBO-ATX trial

By Omar Ford, Staff Writer

Mercator Medsystems Inc. has completed enrollment in its LIMBO-ATX trial. The Emeryville, Calif.-based company's 120-patient trial is designed to use the Bullfrog micro-infusion catheter to test a new treatment strategy to potentially improve blood flow and decrease repeat revascularization procedures in below-the-knee (BTK) critical limb ischemia.

The LIMBO-ATX trial involves the local delivery of an anti-inflammatory steroid, dexamethasone,

See Mercator Medsystems, page 6

Acutus Medical's real-time cardiac imaging catheter wins FDA nod

By Katie Pfaff, Staff Writer

Acutus Medical won FDA approval for its system to create real-time imaging of the heart. The Acqmap high resolution imaging and mapping system and Acqmap 3-D imaging and mapping catheter is indicated for patients undergoing electrophysiology procedures. The device system is anticipated to reach the commercial market in early 2018, with future refinement planned.

"This clearance will allow electrophysiologists [EPs] in the U.S. access to a new technology that uses ultrasound to visualize cardiac anatomy and dipole density to map the pathway of

See Acutus Medical, page 5

First invasive consumables in France admitted to a new reimbursement category

By Bernard Banga, Staff Writer

PARIS – The French authorities have just taken stock of a recently created new reimbursement category for invasive medical devices at the sixth meeting of the French association of medical-device contract research organizations. Invasive

See France, page 7

Appointments and advancements

Irvine, Calif.-based **Biolase Inc.,** a dental laser firm, appointed Richard Lanman, entrepreneur in medical technology, to its board. Lanman steps into the role as Fredrick Moll resigns from the board to fulfill his role as CEO at Auris Surgical Robotics Inc.

Financings

Neurometrix Inc., of Waltham, Mass., closed a $3.5 million private placement of 3,500 shares of series F convertible preferred stock at a price of $1,000 per share that are convertible into 1,330,798 shares of common stock at a conversion price of $2.63 per share. The company's common stock closed on Oct. 30 at $1.80 per share. Proceeds of the offering will be used for commercialization of Quell, the company's over-the-counter wearable device for relief of chronic pain and for general working capital purposes. The closing was the second and final tranche of a $7 million private placement equity offering with a health care dedicated institutional investor reported in July 2017.

Product briefs

Abbott Laboratories, of Abbott Park, Ill., received U.S. **FDA** 510(k) clearance for its Alinity ci-series instruments for clinical chemistry and immunoassay diagnostics. These testing solutions were designed to help the lab more effectively address increases in testing volume. According to the company, benefits include a smaller footprint, improved workflow, reduced wait time and enhanced usability.

Admera Health LLC, of South Plainfield, N.J., reported the launch of multiple laboratory developed tests: Pgxonco, for cancer supportive care, and Liquidgx, a suite of liquid biopsy based tests for tumor profiling and drug resistance monitoring. These newly launched products complement Admera Health's existing tissue based tumor profiling tests.

Avinger Inc., of Redwood City, Calif., received **FDA** 510(k) clearance for modifications to its Pantheris Lumivascular atherectomy system. The 510(k) submission covered a series of nonsignificant design changes already incorporated into commercial products and previously documented as letters to file. The modifications were designed to enhance cutting efficiency, increase product reliability, and improve overall ease of use of the Pantheris system.

Brh Medical Ltd., a Jerusalem, Israel-based developer of products for chronic would care, said it received 510(k) clearance from the **FDA** for its Brh-A2 device. The Brh-A2 is a noninvasive, portable device designed to heal chronic ulcers, reduce lesion size and wound pain by increasing blood flow to the wound. It combines the benefits of therapeutic ultrasound with electrostimulation and modulates them both individually and in combination during the treatment period.

Elixir Medical Corp., of Milpitas, Calif., unveiled its new stent technology, Dynamx, a bioadaptive drug eluting stent (BA-DES) platform at the Transcatheter Cardiovascular Therapeutics conference in Denver. Dynamx is a 71 microns thin cobalt-chromium DES coated with a thin, biodegradable polymer coating that releases Novolimus, an anti-proliferative and anti-inflammatory, that is designed to absorb in six months, restoring the natural pulsatile motion and adaptive remodeling of the artery.

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BioWorld MedTech

BioWorld MedTech (ISSN# 1541-0617) is published every business day by Clarivate Analytics.

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Abbott

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because improvements in technique alone "won't be enough" to close the gap between the GT1 and the company's flagship Xience stent.

The data from both these studies were unveiled at this year's edition of Transcatheter Cardiovascular Therapeutics here in the Mile High City, and the rhetoric suggested that clinicians and trialists see the GT1 as a device that has capably set the stage for a new generation of treatments for coronary artery disease, even if its time has passed. The FDA once again picked a major cardiology conference to unveil a statement about the GT1, noting in an Oct. 31 statement that adverse events were higher with the study article in Absorb III, and oddly recommending that operators choose vessels carefully for adequate diameter despite acknowledging that Abbott has pulled the GT1 from the U.S. market.

The issue of the timing of adverse events related to the GT1 arose at the annual meeting of the American College of Cardiology earlier this year, with the U.S. FDA playing the role of spoiler when it published a physician advisory roughly an hour before the expiration of Abbott's embargo of one-year data from Absorb III. That release of data suggested that thrombosis was more common in smaller vessels up to 12 months, but clinicians speaking on the matter at the time were reluctant to declare the GT1 a technological dead letter. (See *BioWorld MedTech*, March 22, 2017.)

Stephen Ellis of the Cleveland Clinic, a co-principle investigator for Absorb III, reminded attendees at TCT 2017 that the value proposition behind the GT1 was that any increase in problems associated with the device in the early going "would be offset by longer-term results." Ellis said three-year data do a lot to fill in the early clinical picture for most patients, but that this latest batch of data "doesn't inform us on perhaps the most important question," namely, "are our patients better off in the long term?"

Ellis said that follow-up of both arms in Absorb III was roughly 96 percent at three years, at which point target lesion failure was seen in more than 13 percent on the GT1 and 10.4 percent on the Xience. All-cause death numbers were statistically even between the two arms, although the Absorb was numerically better at 3.1 percent compared to 3.4 percent. Cardiac death was likewise statistically indistinguishable, but all infarcts and infarcts due to the target vessel favored the Xience.

Device thrombosis at one year was 2.3 percent for the GT1 and 0.7 for Xience, with a p score of 0.01. However, there was no thrombosis for Xience after 40 days whereas events for the GT1 continued to accumulate out to 36 months. The rate of thrombosis for vessels larger than 2.25 millimeters was substantially lower than is seen in the smaller vessels, but even here, the rate of thrombosis at 36 months was one percent for the GT1, with a large share of those events occurring beyond 32 months.

Ellis added, "there was a lot of interest regarding the 19 percent of patients" who were in Absorb III despite a vessel reference diameter that was equal to or smaller than 2.25 millimeters. He also noted that many operators in the study were implanting the device for the first time, but made the case that follow-up of longer than three years will be needed to determine whether absence of a permanent implant will eventually torque the numbers back toward the GT1.

Thanks to the latest batch of Absorb III data, "we learned that it is probably both" size and procedure that plagues the GT1, adding that about half of the GT1 patients from this study are still on dual antiplatelet therapy at three years.

Stephan Windecker
President, European Cardiovascular Research Institute

Patrick Serruys of Imperial College London pointed to the clustering of thrombosis events between 30 and 36 months, "and that's déjà vu," Serruys continued, perhaps a reference to the late stent thrombosis seen in the first generation of DES devices. Other cardiologists on the dais raised questions such as whether poor device apposition – which drives a lot of the discussion about more aggressive device dilatation – might have fed some of the thrombosis numbers for the GT1, including the notation that more routine use of advanced imaging might have helped with apposition.

Stephan Windecker, president of the European Cardiovascular Research Institute, said that thanks to the latest batch of Absorb III data, "we learned that it is probably both" size and procedure that plagues the GT1, adding that about half of the GT1 patients from this study are still on dual antiplatelet therapy at three years.

Absorb IV

Gregg Stone, co-director of medical research at the Cardiovascular Research Foundation, said the 30-day data from the Absorb IV study provides some insight as to how Absorb III might have offered better numbers for the GT1. This study allowed treatment of up to three lesions instead of the limit of two in Absorb III, and Stone said, "aggressive pre-dilatation and post dilatation was strongly encouraged." He said core labs were charged with putting study sites on hold if operators there implanted in smaller vessels for either device.

Instead of the 2:1 randomization of study article to control device in Absorb III, Absorb IV split the body of enrollees evenly, and Stone said the primary endpoint was met when the GT1 was demonstrated to be non-inferior to Xience for target lesion failure. However, he noted that while reducing the number of small-vessel lesions helped the numbers for the GT1, the lower rate of small vessels also buoyed the numbers for the Xience.

Target lesion revascularization and post-procedural infarct was more commonplace with the GT1 than with the Xience, "and a trend toward greater stent thrombosis was present" for the GT1 as well, Stone said. He said aggressive post-dilatation will help to foster tissue coverage of the device, but concluded, "technique won't be enough. I think it will get us closer" to a Xience-like level of performance, Stone added, but he said inevitably skinnier struts are needed to match the numbers for Xience. ♦

Brazil

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The new rules set higher requirements for class III and class IV devices, while class I and class II devices don't fall under its scope since GMP inspections abroad were already regulated.

"Class I and class II devices already benefit from expedited inspection structures, so RDC 183 will not necessarily affect them. Yet, I believe they will indirectly benefit from it," Benny Spiewak, senior partner at Zancaner Costa, Bastos e Spiewak Advogados, a Sao Paulo-based law firm advising the life sciences sector in Brazil told *BioWorld MedTech*.

"I believe ANVISA is 'done' with the pre-market processes for [class] I and [class] II devices, but manufacturers must keep in mind that post-market surveillance will be, from now on, the main regulatory focus. Also, specific certifications such as INMETRO, INCQS and other regulatory (approvals) required will remain mandatory to keep a simplified registration (cadastro) valid," said Gabriel Vieira, LatAm regulatory affairs manager at Philips Latin America.

The new regulation for GMP inspections abroad applies to manufacturing plants located outside Brazil and the Mercosur area that produce end products, in their name or on behalf of another company. It also applies to manufacturing plants carrying out the final product releases associated with at least one production step, excluding design, distribution, sterilization, packaging and labeling steps. The regulation also applies to medical software manufacturing units.

"[The new regulation] aims at improving the dynamics of GMPs certifications and seems to clear the way for ANVISA to further harmonize its policies with other agencies," explained Spiewak.

The med-tech manufacturers with a presence in Brazil praised the regulator's move.

"Impacts are likely to be positive in my opinion. We have now a more complete and clear requirements set for deliverables, documents and information to be provided to ANVISA on the GMP submissions," said Vieira. "Philips receives and views it as a good advance in the regulatory landscape for Brazil. I believe this will help ANVISA to be in a good shape with the most recent global regulations and to put effort on what really matters: device safety, risk management, post-market surveillance and, most important, population safety," he added.

Existing backlogs played an important role in triggering this new regulation, according to Spiewak. With GMP audits and processes stalled in ANVISA's queue, the move from the regulator aims to clear the waiting list and skip having to go through the Brazilian judiciary system, which has played a key role in GMP inspections in the past few years, while bringing uncertainty to the med-tech business.

"[The regulation] is also the baseline for the decision to have an onsite inspection or not, based on not only documentation, but also the risks involved (considering the devices categorization, post-market surveillance information, etc.). This will be key to allow the ANVISA backlog to be resolved once for all," said Vieira.

Implementation will take time

Consultants like Spiewak are not very enthusiastic about the immediate results of the new regulation. His prediction is that the results to clear the backlog are, at least, one year away.

"A company needed to allot at least three years to consider its inspection. Courts became part of the game, which produced almost unbearable levels of unpredictability, which rarely helps business or attract business," explained Spiewak.

But behind ANVISA's new regulation, there's also a harmonization strategy.

"ANVISA is quite active when it comes to international harmonization initiatives. Yet, it was a late adopter of such harmonization plans. RDC 183 seems to point to a more proactive approach," said Spiewak.

"Hopefully, we will come to a point where an approval by the Canadian or U.S. agency would lead to automatic or quasi automatic approval by ANVISA," added Spiewak.

For its part, Vieira recognized the importance of the harmonization aspects that this new regulation creates in Brazil. "This is the first step towards harmonization of requirements in a global level and a clear path to focus in risk. It is a good initiative from ANVISA to go on the same direction as the U.S. FDA and other regulatory agencies," he said.

In fact, the new regulation contains a disposition for petitions relating to manufacturers currently participating in the Canadian Medical Devices Conformity Assessment System (CMDCAS) and qualifying for the Single Health Products Audit Program (MDSAP), giving them 60 days to provide valid proof of their participation in the CMD-CAS program, demonstrating that the company complies with its requirements to get their GMP certification.

Brazil is a member of the International Medical Device Regulators Forum (IMDRF), along with Australia, Canada, China, the European Union, Japan, Russia, Singapore and the U.S.

"ANVISA plays an important role on the IMDRF group," said Vieira. "Last year both sessions happened in Brazil [Brasilia and Florianopolis]. I had the opportunity to attend both events and the impressions are good. The dialogues seem to be productive and we are seeing results not only in MDSAP, but also in the UDI, RPS and other related in the IMDRF discussions. Most important: They are giving visibility to the regulated sector to track what is really going on," said Vieira. ♦

Acutus Medical

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every heartbeat. The system also can be used with existing commercially available cardiac ablation platforms," said Steven McQuillan, senior vice president, regulatory and clinical affairs, Acutus Medical.

Carlsbad, Calif.-based Acutus brings together an ultrasound imaging and non-contact mapping of each heart beat's electrical conduction in the Acqmap system, enabling identification of arrhythmias throughout the chamber. "For the first time Acqmap allows physicians to see real time continuous mapping of the whole atrial chamber and activation of the heart," McQuillan told *BioWorld MedTech*. "If a patient has atrial fibrillation [AF] or tachycardia, [an EP] will be able to see the whole heart," he explained.

External and internal cardiac imaging

While an ultrasound device creates imaging of the heart's anatomy, the system also provides an interior view with non-contact electrodes which "map the heart." "In the same way that ECG gives pictures of the outside of the heart, this is the same concept but inside the heart," said McQuillan. Acqmap can create a "higher resolution and more accurate picture of what is occurring in the heart." The system also creates images more quickly and often. Unlike standard catheter imaging technology, which takes about 20 minutes to generate an image of the heart, according to McQuillan, Acqmap can provide a continuous, real-time image that is mapped in four seconds, making it a useful tool during procedures.

FDA clearance, as well as use in Europe, was based in part on data from the DDRAMATIC-SVT trial. Feasibility data was presented in a 2016 American Heart Association presentation, "Abstract 17822: Initial procedural results from the DDRAMATIC SVT Study: AF mechanism identification and localization using dipole density mapping to guide ablation strategy." Research across six sites between January and May 2016 included 27 enrolled patients. Using pre-ablation maps, 167 mechanisms were identified (an average of 6.2 per patient), including 40.2 percent irregular reentry, 31.1 percent focal, 28.7 percent rotational activation. According to the study conclusions, "Identifying and targeting actual AF mechanisms for ablation using dipole density is feasible. Pre-ablation maps identified rotational, irregular reentrant, and focal activation patterns. Targeted ablation of mechanisms altered conduction and/or resulted in AF conversion. Long-term outcome data is needed."

Better arrhythmia ablation

"The Acqmap system clearance represents a step not seen since the inception of 3-D mapping systems 20 years ago," said Graydon Beatty, CTO, Acutus Medical. "Despite decades of procedural and technical advancement in the electrophysiology field, only about 50 percent of patients with persistent complex atrial arrhythmias treated with ablation therapy can expect to remain arrhythmia free at 12 months. At Acutus, we think better mapping and the ability to re-map during the initial therapeutic procedure has the potential to lead to better outcomes and quality of life."

> *"The Acqmap system clearance represents a step not seen since the inception of 3-D mapping systems 20 years ago.*
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> Graydon Beatty
> CTO, Acutus Medical

Acqmap; Acutus Medical

Real-time non-contact mapping provides a safe method for analysis of heart conditions diagnosed by an EP. "The Acqmap system was designed in collaboration with some of the most respected names in the field to provide practitioners with a suite of tools that enables them to rapidly map and re-map to visualize changes throughout the ablation procedure," said McQuillan. The system also can assist during ablation procedures and illuminate changes to the heart from treatment.

Collaboration, competition

Tom Wong, Royal Brompton Hospital, London, shared that the facility has begun using the devices in treatment of arrhythmia. "The Acqmap system is able to provide global dipole density mapping of irregular and chaotic activation in the atrial chambers, whereas conventional sequential mapping may struggle to provide us with the information that is required. In the cases we have performed thus far, real-time mapping of complex arrhythmias has allowed us to focus on areas of interest and terminate the arrhythmia using ablation therapy. We can now offer individualized, tailored therapy, and are one step closer to identifying the mechanisms of complex arrhythmias."

Mason, Ohio-based Atricure also markets its Synergy ablation system to treat AF while Boston-based Luxcath LLC is developing a cardiac ablation visualization and optical tissue interrogation device. (See *BioWorld MedTech*, April 13, 2016.) Advanced Cardiac Therapeutics Inc., of Santa Clara, Calif., offers a next generation ablation catheter for treatment of cardiac arrhythmia, which uses temperature, electrogram imaging and contact to monitor treatment effects during an ablation procedure. (See *BioWorld MedTech*, May 3, 2017.) ♦

Mercator Medsystems

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in an attempt to stop this scar tissue buildup and keep blood flowing.

"We're trying to treat the inflammation associated with the mechanical revascularization, to change the way the vessel heals and to limit restenosis," Trent Reutiman, CEO of Mercator Medsystems, told *BioWorld MedTech*.

The Mercator Bullfrog micro-infusion device has received FDA clearance and CE mark. The technology infuses therapeutic and diagnostic agents directly, non-systemically, and safely through blood vessel walls into adventitial tissues.

"If we want to use a specific drug for an additional indication like improving patency in BTK interventions, then we would have to do a randomized study like [LIMBO-ATX]," Reutiman said. "We want to get data so that we can add that indication or complication to the device's labeling."

Positive results from the study can be used by the company to seek new indications for the use of Bullfrog to deliver the generic steroid dexamethasone for patients with CLI to improve the outcomes of revascularization alone.

Reutiman added, "[the study] is a little unique in that you would have drug labeling that could potentially reside inside the device instructions for use, for example."

The primary follow up endpoint is an angiographic – a visual endpoint of the target lesion. This image would be taken six months after the treatment.

"We really anticipate having the data back from this randomized controlled IND study in April or May of 2018," Reutiman said. "Then we'll be submitting the data to the FDA."

Mercator previously sponsored the DANCE trial, which reached its primary endpoint in early 2017. The DANCE trial demonstrated positive patency outcomes with Bullfrog delivering dexamethasone in combination with angioplasty or atherectomy in above-the-knee endovascular revascularization.

"We believe Bullfrog is a platform technology, and it is approved for any drug or biologics delivery in the peripheral or coronary now," Reutiman said. "As long as the material can pass through a 34 gauge micro needle, then this really is a drug delivery platform for any drug that there would be a benefit for delivering locally, rather than say systemically."

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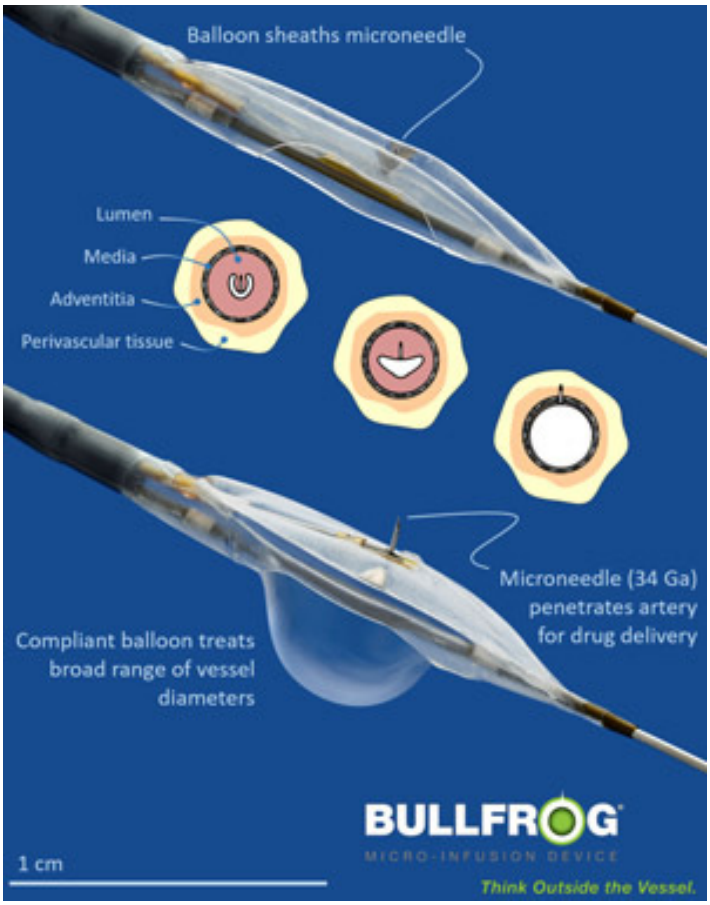

Bullfrog micro-infusion device; Mercator Medsystems Inc.

Upsetting the BTK/DCB paradigm

Much of the drug delivery in coronary and peripheral vascular arteries is through drug-coated balloons (DCB) and stents. Bullfrog could potentially compete against these devices, particularly DCBs, Reutiman said.

Medtronic plc had a couple of failed trials in BTK peripheral arterial disease (PAD) with its DCB technology.

The Dublin, Ireland-based company is giving it another shot with a small, European study using improved technology and clinical trial design. The results, expected in 2020, could offer initial evidence that DCBs can provide enough long-lasting vessel patency to improve wound healing in tough-to-treat patients.

Becton, Dickinson & Co., through its $24 billion acquisition of C.R. Bard, is the only company with an ongoing IDE trial for a DCB in arteries BTK. (See *BioWorld MedTech*, April 25, 2017.) Bard gained access to drug coated balloons when it acquired Minneapolis-based Lutonix Inc. for $225 million in 2011. (See *BioWorld MedTech*, Dec. 21, 2011.) The device received approval in 2014. (See *BioWorld MedTech*, Oct. 13, 2014.)

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France

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medical devices removed after operations – such as probes, certain types of stent, and balloons – were not specifically reimbursed in France.

"A year ago, only medical devices implanted in whole and remaining in the human body longer than 30 days had a specific reimbursement category on the list of services and products qualifying for reimbursement," André Tanti, vice-president of the French economic committee for health care products, responsible for the medical-device section, told *BioWorld MedTech*.

According to a new report by the French general inspectorate of social affairs, at least a dozen categories of interventional medical technology required specific reimbursement, i.e., not included and buried away in each hospital stay-related group. "These are essentially medical devices used during measurement, control and guidance procedures, as well as to deliver active principles," said Etienne Marie, the French inspector general of social affairs who wrote the report. Such devices include drug-coated balloons, ablation probes for atrial fibrillation foci, fractional flow reserve measurement devices used during cardiac catheterization, cortex perforation guidance devices for inserting screws during spinal-column surgery, mechanical thrombectomy devices and radio-frequency renal denervation devices.

No fewer than around 20 European and U.S. manufacturers expressed their interest under the aegis of SNITEM, France's national trade organization for the medical-technology industry. In 2013, this led to a commitment from the French prime minister as part of a contract for the health care industry. Nevertheless, it took until the end of 2015 for a decree to appear launching this new reimbursement procedure in France. This year, an order dated May 4 established two eligibility criteria for this new category V: medical devices must be invasive (i.e., penetrate, partly or in whole, inside the human body through a body orifice or the surface of the body) and must be implanted by a doctor. "This category does not reimburse all expensive consumables, only those that are truly innovative as well as costly," said Tanti. Nevertheless, kits and accessories enabling such medical devices to be used are not reimbursed.

12 medical devices admitted over the past six months

A dozen products have received a favorable opinion from the French national commission for assessing medical devices and health care technology (CNEDiMTS) in four main categories:

- Stent retrievers used during thrombectomies to treat acute ischemic strokes: Solitaire II and Solitaire Platinum stents from Medtronic plc, Trevo Provue and Trevo XP Provue stents manufactured by Concentric Medical Inc. and distributed in France by Stryker Corp.
- Coronary balloons such as the Ranger drug-coated balloon from Boston Scientific Corp.
- Peripheral drug-coated balloons for femoral arteries: the paclitaxel-coated In.Pact Admiral drug-eluting balloon from Medtronic, the Lutonix 035 balloon from C.R. Bard Inc., the Stellarex balloon from Spectranetics Corp., the Sequent Please NEO balloon from B. Braun Medical AG, and the Ranger balloon from Boston Scientific Corp.
- Bronchial thermoplasty catheters: the Alair bronchial thermoplasty catheter from Boston Scientific Corp.

> *"The new reimbursement category is paving the way for valuing novel invasive medical devices implanted for less than 30 days at a specific tariff negotiated with the French authorities.*
>
> André Tanti
> Vice president, medical devices, French economic committee for health care products

According to the French National Authority for Health, a total of 30,000 patients a year could benefit from these medical devices, which are completely reimbursed by the new reimbursement category. And things are not yet finished. "We've just create a new section for fractional flow measurement devices, for which we're currently assessing three medical devices," said Tanti.

French ministries of health and economy have the final say

Manufacturers submit their applications to the French National Authority for Health, with a view to their medical devices being assessed for brand-specific reimbursement under the new category V.

"Medical technology is assessed in the same way as other categories on the list of services and products qualifying for reimbursement, with an administrative processing delay of 180 days maximum once an application has been accepted. We particularly insist that specific clinical data for the invasive medical device, comparing it to the reference technique, must be available. This is because a medical device is meant to improve a procedure," said Hubert Galmiche, deputy head of the medical-device assessment department at the French National Authority for Health.

Listing in the new reimbursement category V is limited to novel medical devices providing major, significant or moderate added clinical value (ASA I, II or III).

The final decision is made by the French authorities, in particular by the ministries for health and the economy. They can decide not to list a medical device in category V despite a favorable opinion from the CNEDiMTS, the independent assessment authority. The French authorities justify their refusals on the basis of low added clinical value. For example, they decided not to admit the Ranger drug-coated balloon and the Alair bronchial thermoplasty catheter from Boston Scientific Corp. to this new reimbursement procedure. "The added clinical value of the coronary balloon was level 5 (no added clinical value) compared

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Mercator Medsystems

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Reutiman said if the data bears fruit, then Bullfrog could have somewhat of an advantage over DCBs.

"Unlike a stent or a balloon, we can deliver as much drug through multiple microinfusions with one catheter as needed to treat a short lesion or a long lesion," said Reutiman. "We're not wed to the shape or size of the balloon or the stent to where you're delivering a drug."

Small investments lead to growth

Mercator was founded in 2001 and has raised very little money in its first 12 to 14 years. Reutiman quipped that the company has had "micro investments."

"On very little investment, with just a couple of [people on staff], the company was able to work out a lot of intellectual property and a lot of broad regulatory approval for the device," Reutiman said.

In 2013, the company raised about $6.5 million in a series B round. Reutiman said there are plans for an upcoming series C round.

"We really hope to lead the way in below-the-knee drug delivery," he said. "A lot of that speaks to the efficacy of the device in delivering drug to [below the knee]. It's a different drug approach." ♦

France

Continued from page 7

to coronary stents in category III. The added clinical value of bronchial thermoplasty catheters was level 4, which corresponds to minor added clinical value," said Tanti.

Greater transparency on expensive consumables

There are many advantages to this new reimbursement procedure. "Hospitals will no longer have to limit using such expensive innovative technology for budgetary reasons alone," said Galmiche. Manufacturers of innovative medical devices implanted for less than 30 days enjoy a tariff value on a special reimbursement list (the additional list) and French hospitals are completely reimbursed. Retriever stents have been valued at $3,312 each. For the French authorities, this new reimbursement procedure will enable expensive consumables to be individually monitored in administrative databases via their codes on the list of services and products qualifying for reimbursement. This provides the twofold benefit of medical-device vigilance/procedure analysis and budget monitoring.

For the time being, "this barrier to entry has helped clean up the stent-retriever market," said Tanti. Only three products have been assessed, whereas there are a dozen stent retrievers on the French market. According to Faraj Abdelnour – president of the association of European medical-device industry managers (ACIDIM) – non-reimbursed products must obviously "stop being marketed in France and move onto markets without barriers, such as Germany." The fact remains that creating this new reimbursement procedure will generate additional expenditure. The French ministries for health and the economy, as well as the French social security department, prefer not to give any figures to avoid causing a 'knock-on effect' and windfall effect that could increase applications for category V. ♦

Product briefs

Glooko Inc., of Mountain View, Calif., reported the results of a feasibility study that examined the impact of Glooko's product, the Mobile Insulin Dosing System (MIDS) on glycemic control of people with type 2 diabetes on long acting insulin. MIDS is currently available for investigational use only. In this feasibility study, Glooko evaluated the extent to which its MIDS for long-acting insulin (LAI) dose adjustment can help people with type 2 diabetes, make appropriate titration adjustments and improve their glycemic status. The feasibility study, although only for a three week duration, showed that participants experienced the following clinical results as a result of using MIDS: The mean blood glucose level of participants decreased on average by 18.2 mg/dL; the proportion of in-range blood glucose readings (defined as 80-180 mg/dL) of participants increased by 9 percentage points; the percentage of hyperglycemic events (defined as readings >250 mg/dL) of participants decreased from 14.1 percent of readings to 3.2 percent; and the recommended LAI dose increased by 18.7 percent from the initial dosage by the end of the study period ($p = .013$) on average.

Ivantis Inc., Irvine, Calif.-based developer of the Hydrus microstent, a device designed to lower eye pressure for open-angle glaucoma patients, said it has submitted its final premarket approval module, which uses data from its HORIZON pivotal trial, to the U.S. **FDA** for market approval. HORIZON is a 556 patient, prospective, randomized trial conducted at 38 centers in nine countries. Patients were followed for two years. Study subjects with mild-to-moderate primary open angle glaucoma underwent cataract surgery. At the time of surgery, subjects were randomized to receive either cataract surgery alone, or cataract surgery plus the Hydrus microstent. Roughly the size of an eyelash, the Hydrus microstent is a next-generation minimally invasive glaucoma surgery device designed to reduce eye pressure by reestablishing the eye's natural outflow pathway, known as Schlemm's canal.

Product briefs

Jubilant Draximage Inc., of Quebec, received **FDA** approval for the extension of the in-use shelf life of Draximage Maa (kit for the preparation of technetium Tc 99m albumin aggregated injection) to 12 hours post-reconstitution. Draximage Maa is a lung imaging agent, which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and pediatric patients.

Omnilife Science Inc., of Raynham, Mass., has begun clinical evaluations of its exclusive Omnibotics active spacer robotic tissue balancing device at three U.S. sites. This technology received 510(k) clearance from the **FDA**, Sept. 1. The Omnibotics active spacer, in clinical use since March in Australia, provides the surgeon with a quantitative tool to actively manage the soft tissue envelope with dynamic real-time feedback. When combined with the accuracy of alignment and bone cuts provided by the Omnibotics system, the result is a completely customized procedure from both a skeletal and a soft tissue perspective.

Procept Biorobotics, a Redwood Shores, Calif.-based surgical robotics company developing technologies to treat prostate disease, reported the first commercial Aquablation procedures have been completed in Germany. Aquablation combines the clarity of real-time, multidimensional imaging with the accuracy of an autonomous robot and the power of a heat-free waterjet for targeted and precise removal of excess prostate tissue. Additionally, the company has initiated the FRANCAIS WATER (French Aquablation Clinical Investigation using Waterjet Ablation Therapy for Endoscopic Resection of prostate tissue) clinical trial, a necessary first step in gaining reimbursement for the company's Aquabeam system in France. The single arm, multicenter prospective trial will determine the safety and efficacy of the Aquabeam system in the treatment of benign prostatic hyperplasia in men 45 to 80 years of age.

Sensus Healthcare Inc., Boca Raton, Fla.-based provider of noninvasive treatment of nonmelanoma skin cancers and keloids with superficial radiation therapy (SRT), said the SRT-100 is now cleared for sale in Mexico. The system is approved for the treatment of nonmelanoma skin cancer and keloids and will be placed on the National Registry upon its next publication by February 2018. Sensus has engaged Cyber Robotics of Mexico City as its distribution partner.

Wright Medical Group NV, of Memphis, Tenn., and Middlesex U.K., reported the first patient implanted in the U.S.-based Infinity total ankle system follow-up study at the Campbell Clinic in Memphis, Tenn. The primary objective of the multicenter, nonrandomized, prospective study of 200 patients is to evaluate 10-year implant survivorship in patients with ankle joints damaged by severe rheumatoid arthritis, post-traumatic arthritis, or degenerative arthritis who received the Infinity total ankle system for primary ankle arthroplasty.

Other news to note

Cep America Inc., of Emeryville, Calif., has launched its Acute Neurology practice, a single solution for the integration of teleneurology, telestroke, neurohospitalist, neuro-diagnostic and other neurology specialty services. Cep America expanded into Acute Neurology when the physicians of SAGE Neurohospitalist Management Group joined the partnership in July 2017.

Clarify Health Solutions Inc., of San Francisco, unveiled a bundled payment and population risk management platform. The significant expansion of Clarify Health's value-based care technology solutions addresses several industry pain points. The Centers for Medicare & Medicaid Services is expected to announce new, voluntary bundled payment programs in the coming months.

Edwards Lifesciences Corp., of Irvine, Calif., reported new data demonstrating substantial economic advantages of the Edwards Sapien 3 transcatheter aortic heart valve for patients suffering from severe, symptomatic aortic stenosis (AS) who are at intermediate risk for open-heart surgery. Results of the economic analysis, which is the first-of-its-kind report on intermediate-risk patients, were presented as a late-breaking clinical trial at the 29th Transcatheter Cardiovascular Therapeutics, the annual scientific symposium of the Cardiovascular Research Foundation, in Denver. The economic analysis of the Sapien 3 valve compared to surgery involved more than 2,000 patients enrolled in both the PARTNER II A trial and the Sapien 3 intermediate risk trial. The analysis showed significantly lower total one-year costs, on average, with the Sapien 3 valve compared with surgical aortic valve replacement ($80,977 vs. $96,489). Average index hospitalization costs, which include the costs of the procedure, hospital stay and physician fees, were also lower with the Sapien 3 valve vs. surgery ($54,256 vs. $58,410). Reduced length of stay, simpler, more efficient procedures, fewer repeat hospitalizations, and less time in rehabilitation contributed to the economically dominant results of the Sapien 3 valve. Transcatheter aortic valve replacement with the Sapien 3 valve added 0.27 quality-adjusted life years per patient at a lifetime cost savings of about $10,000 compared with surgery.

Neurovive Pharmaceutical AB, of Stockholm, Sweden, has signed a collaboration agreement with Kevin Wang of the University of Florida to conduct biomarker research for Neurovive's traumatic brain injury (TBI) program. The research is aimed at developing alternative endpoints for the company's clinical TBI program by analyzing patient samples from the previously completed CHIC study. The research will evaluate the use of biofluid-based biomarkers in TBI drug development, which is increasingly recognized as being of utmost importance for diagnosis, prognosis and therapy evaluation.

As part of its ongoing commitment to increase the utility of next-generation sequencing in the clinic, **Thermo Fisher Scientific Inc.**, of Carlsbad, Calif., has expanded the development of its Oncomine Dx Target Test by entering into an agreement with **Blueprint Medicines Corp**., of Cambridge, Mass., to develop and commercialize the Oncomine Dx Target Test as a companion diagnostic (CDx) for BLU-667 to identify RET fusions in people with non-small-cell lung cancer. Thermo Fisher will also retain the rights to commercialize the test and will lead all necessary filings to seek clearance from regional regulatory agencies for the test. Expansion of the CDx is part of a strategic plan to develop one test for multiple therapies.

Oncology Extra

Keeping you up to date on recent developments in oncology

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

Curie temperature reset may bring hyperthermia back to oncology

Medical science has previously attempted to beat cancer by making life too hot for cancer cells, but these efforts faltered due to problems with temperature regulation. That problem might be a thing of the past, thanks to research conducted at the University of Surrey in the U.K. and Dalian University of Technology in China. This group of researchers saw the chemical stability of cobalt-zinc (Co-Zn) ferrite nanoparticles as a good place to start, but the addition of chromium to this construct appears to render a nanoparticle that won't heat to temperatures any higher than 45°C (113°F), which is cool enough to avoid serious damage to adjacent, healthy tissues. This is still a preclinical study, but an in vitro experiment confirmed that these magnetic nanoparticles should not be toxic to healthy human tissue and should be sufficiently thermally self-regulating that they could quickly kayo a number of cancers. The article explaining this research appears Oct. 20, 2017, in the online issue of *Nanoscale* under the title "Novel nanoparticles with Cr3+ substituted ferrite for self-regulating temperature hyperthermia."

Lymph node ratios for PNET staging

Nodal positivity is pretty much the standard for stating pancreatic neuroendocrine tumors (PNETs), but there is evidence that the lymph node ratio (LNR) is a more useful instrument for this kind of effort. A retrospective analysis of data for nearly 900 patients who underwent a pancreatectomy with lymphadenectomy between 2004 and 2011, drawn from the Surveillance Epidemiology End Results database, checked for disease-specific survival (DSS). Several parameters were associated with lower DSS, including age greater than 57 and the presence of distant metastases using a univariate analysis, and a multi-variate analysis suggested that men aged 57 or older, those with distant metastases, and a history of partial pancreatectomy were likewise associated with lower DSS. The analysis of LNR and nodal positivity, however, suggested that a reading of at least 0.5 predicted outcomes independently of other factors, and hence is at least possibly a better measure for staging purposes than the current AJCC staging system. This analysis appears Oct. 20, 2017, in the online edition of the *Journal of Clinical Endocrinology & Metabolism*, under the title "A lymph node ratio-based staging model is superior to the current staging system for pancreatic neuroendocrine tumors."

MHC and antitumor immunity 1

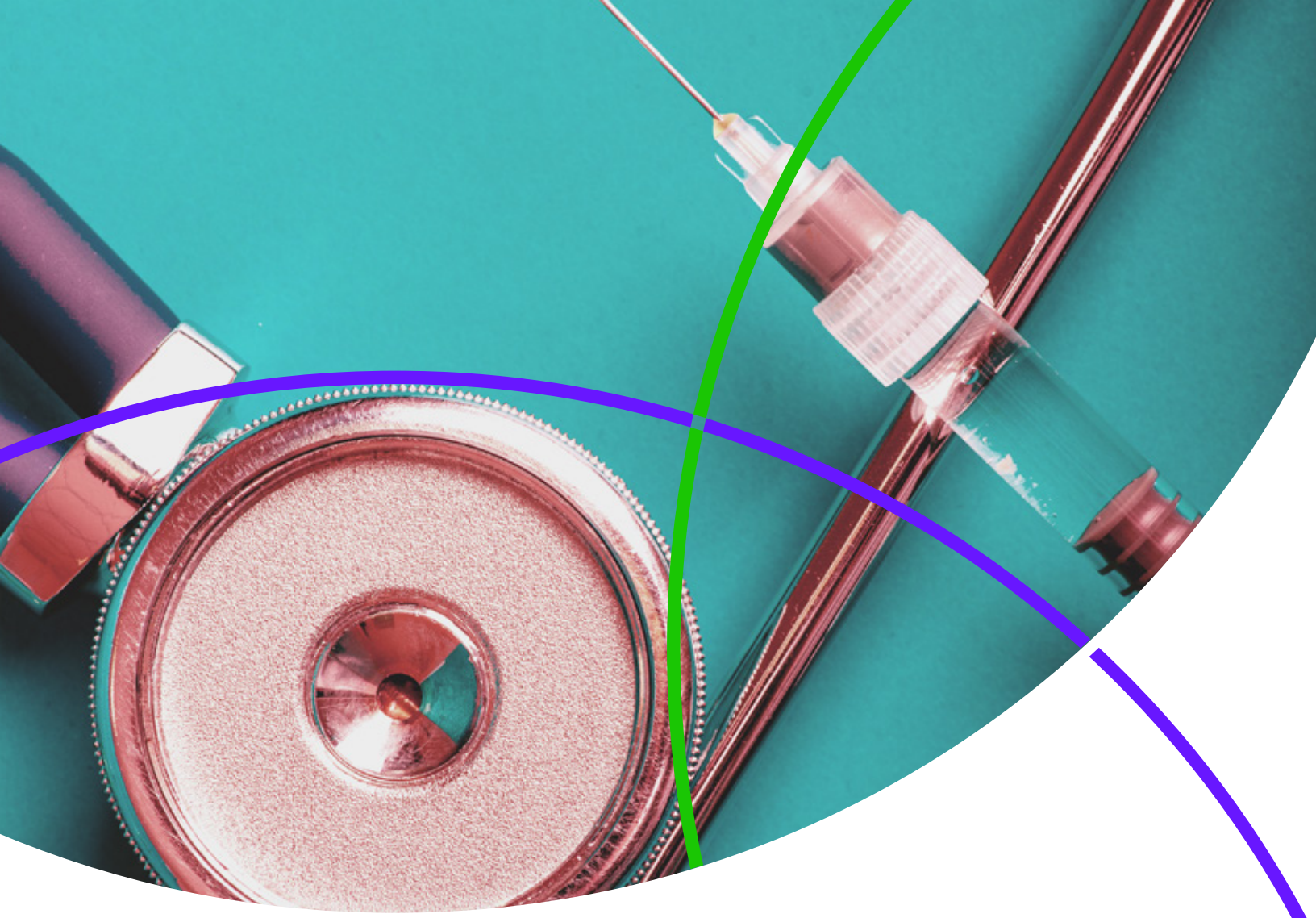
Researchers from the Fox Chase Cancer Center have developed a method to study the effects of major histocompatibility complex class 1 (MHC-1) type on the presentation of tumor antigens, and shown that MHC-1 type influenced the presentation of tumor antigens. The team looked at the relationship between MHC-1 type and antitumor antigen repertoire of more than 9,000 patients, and showed that "MHC-I genotype-based scores could predict which mutations were more likely to emerge in their tumor." As one would expect, "poor presentation of a mutation across patients was correlated with higher frequency among tumors. These results support that MHC-I genotype-restricted immunoediting during tumor formation shapes the landscape of oncogenic mutations observed in clinically diagnosed tumors and paves the way for predicting personal cancer susceptibilities from knowledge of MHC-1 genotype." The team published its findings in the Oct. 26, 2017, issue of *Cell*.

MHC and antitumor immunity 2

A separate team of researchers has shown that late during tumor evolution, another mechanism comes into play, namely loss of heterozygosity (LOH). LOH is the loss of one copy of a gene. Because MHC genes are among the most diverse in the genome, losing one copy reduces the breadth of the immune system's response to tumors. Researchers from the British University College London and the Tracking Cancer Evolution through therapy (Rx) (TRACERX) consortium have analyzed tumor evolution during treatment in non-small-cell lung cancer (NSCLC) patients and found that nearly 40 percent of tumors showed LOH, that LOH tended to occur late in tumor evolution, and that it appeared to be under strong microenvironmental selection pressure. The team noted that "our results may . . . have implications for vaccine- and T-cell-based therapeutic approaches, specifically targeting neoantigens, with up to 92 percent [of] predicted neoantigens in one tumor found to bind the lost [gene copy]." Those results appeared in the Oct. 26, 2017, issue of *Cell*.

HIFU applied to pediatric osteoid osteoma

A cancer does not have to be metastatic to be a life-altering experience, but physicians at the Sheikh Zayed Institute for Pediatric Surgical Innovation at Children's National Health System have wrapped up a pilot clinical study that demonstrates that MR-guided high-frequency ultrasound (MR-HIFU) can safely treat this condition in children and adolescents. The study of nine patients between the ages of six and 16, matched with nine historical controls treated with CT-guided RF ablation, demonstrated that the new modality capably treats the condition while avoiding the drilling into the body that goes with CT-guided RFA. In addition to the pain incurred during this standard of care, both patient and operator are exposed to radiation, but the procedure also carries some risk of infection. MR-HIFU is also a shorter procedure, getting patients out of the clinic and back home more rapidly than is possible with the standard of care. The article explaining this pilot study appears in the *Journal of Pediatrics* under the title "Comparison of noninvasive high-intensity focused ultrasound with radiofrequency ablation of osteoid osteoma."



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