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Can New Wave Of Tests Finally Nail Early Diagnosis Of Lung Cancer?

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The five-year survival rate for lung cancer remains a dismal 17.7%, a rate that improved only by a few percentage points since the 1970s, largely because most cases are still diagnosed in late stages. The disease is also common, being the second-most frequently diagnosed cancer in the US and the most diagnosed kind in China, where smoking is on the rise among young adults.

Catching lung cancer early is paramount to improving the survival rate and reducing treatment costs. Early-stage lung cancer, often picked up as an "incidentaloma" on CT scans ordered for other reasons, has a five-year survival rate of 55%, compared with only 4% at stage 4.

While many liquid-biopsy companies offer approaches to treatment selection and prognostication for diagnosed lung cancer, other device companies are honing in on the early diagnostic space for this disease, where they see two important unmet needs.

The first, quite simply, is early detection. The current gold standard is low-dose CT scanning (LDCT) in high-risk populations, a strategy that gathered momentum after a landmark 2011 study appeared in the *New England Journal of Medicine*. The National Lung Screening Trial (NLST) demonstrated a 20% mortality reduction in lung cancer with LDCT screening programs for patients aged 55 to 80 with a history of 30 pack-years of smoking or more who are either current smokers or who quit 15 years ago or less. Some nine million people in the US are eligible for screening based on the NLST criteria.

There are drawbacks to LDCT, including cost, risk of radiation, and false positives. Most countries outside the US can't afford to institute widespread CT screening, and many centers in the US do not yet follow guidelines. Moreover, over half of lung cancers still occur in people who don't meet strict LDCT screening criteria. "Even if 100% of the people who met that criteria actually went and got screened, they'd still miss the majority of lung cancers," says Barry Cohen, director of sales at **Genesys Biolabs**, which markets an early-detection blood immunoassay.

LUNG NODULE HEADACHES

Another drawback, one that causes a second major unmet need, is the indeterminate nodule. While many nodules found on CT, either incidentally or through a screening program, can be categorized as high- or low-risk (based in part on size and patient risk factors), leading to straightforward next steps, others fall into a gray area.

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FROM THE EDITORS OF: **THE GRAY SHEET, CLINICA, START-UP** AND **MEDTECH INSIGHT NEWSLETTER**

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and the US agency consistently apply benefit-risk factors in making decisions about nonconforming products on the market and regulatory compliance issues. It is part of FDA's larger effort to harmonize risk-benefit standards throughout the agency's device center.

COMMERCIAL

START-UP SPOTLIGHT

Device Manufacturers See 'Irreparable' Harm In Indian Draft Regulations

PENELOPE MACRAE

Until recently, India's government has not put the medical device industry under as much regulatory scrutiny as other sectors, causing concern over the safety and efficacy of such products. But the government has now drafted a wide-ranging set of medtech regulations that it expects to "notify" soon, without waiting for the nod of India's fractious Parliament.

While device-makers have welcomed the move to better regulate the industry as an overall positive step, they're also pushing for the government to take a second look at the draft rules, saying some could cause more problems than they solve.


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CALL FOR CLARITY

The rules, which come after lengthy discussions between industry players and the Indian government, "need more clarity and alignment with global best practices to fully meet the sector specific requirements in order to ensure predictability in the Indian market, which is a critical factor when it comes to investment decisions," said Varun Khanna, a leading official of the India arm of US-based medical device trade association AdvaMed.

The Medical Technology Association of India (MTaI) said in a Dec 20 statement that "logjams on some key issues pertaining to the industry at the policy level are likely to do irreparable damages." MTaI members have made significant investments in India by setting up manufacturing and R&D operations and include big names such as **Boston Scientific Corp., Johnson & Johnson and Medtronic PLC**.

India is already one of the world's 20 biggest medical device markets and Asia's fourth-largest after South Korea. Thanks to an expanding middle class, aging population, widening insurance coverage and government universal health-care initiatives, the growth potential is huge, says a 2016 report by consultancy Deloitte entitled *Making in India - A Leap For Indian Healthcare.*

Key to attaining that growth, though, is to get the regulation right, say device-makers. With an enabling, transparent and predictable policy framework and ecosystem support, the country's device industry could be worth $25-30bn or even more by 2025, up from $3.7bn in 2014, predicts the report. Some industry estimates indicate a potential to grow at around 28% a year to $50bn by 2025.

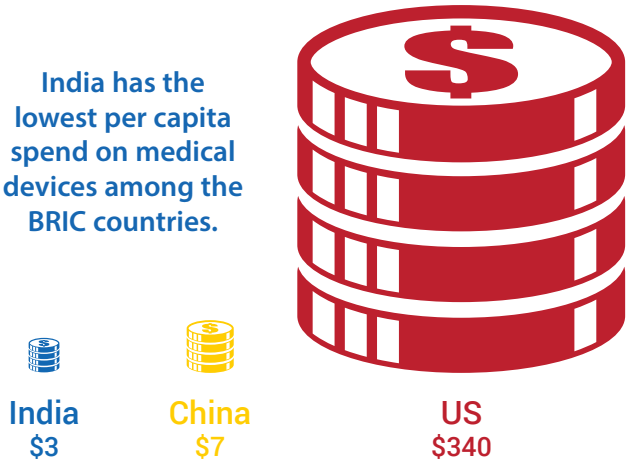
India's per-capita spend on medical devices is the lowest among the BRIC countries at $3, compared with $7 in China; in the US, it's a whopping $340.

GLOBAL HARMONIZATION BACKBONE

At the top of the regulatory must-do list, say device firms, is for the *globally harmonized definition of medical devices to be included in the new Indian regulations. Harmonization principles established by the Global Harmonization Task Force and advanced in recent years by the* International Medical Device Regulators Forum, along with risk-based classification, "needs to be the backbone of rules," said Khanna, who's also India and South Asia executive managing director of global medical technology BD India.

India's medtech spend per captial vs China and US

India has the lowest per capita spend on medical devices among the BRIC countries.



Nearly all the top 40 global medical devices firms have an Indian presence, but most have their production base outside India and import their products for the Indian market. Right now, the country imports at least 70% of its medical devices – from implantable devices to robotics – and there are fewer than 60 domestic medical device companies out of around 750 with annual revenues of more than $10m.

Understandably, Prime Minister Narendra Modi's government, which wants to create jobs for its army of young people, is keen to change that picture. Harmonizing with global standards would be the best way for the government to promote "Make in

India" in the sector, say device-makers, as it would make it easier for companies to design, develop, male and test products in India and be part of the global supply chain.

The government has already instituted a 100% automatic direct investment route in the sector to push local manufacture.

REALISTIC TIMETABLE FOR UDIS

Another problem area in the draft rules, says the industry, is the plan to introduce UDIs (Unique Device Identifiers) for medical devices. The decision is welcome but the government's call for "every medical device to have a UDI from 2017 in India is not feasible as companies will not be in a position to do so only for India," said Probir Das, MTaI member and managing director of Terumo India.

UDI is being rolled out "in a stage-wise process in the United States and European Union as per the classification of the device," he noted, and India should follow their lead.

Device-makers are also concerned about a move to limit shelf life to five years for all medical devices. "Devices unlike drugs – which are chemical entities – are more stable," said Sushobhan Dasgupta, managing director of Johnson & Johnson Medical. "There's no reason to restrict shelf life to five [years]…for those devices where a shelf life of 10 years is globally accepted," he said.

Device companies are also unhappy about a proposal calling for clinical investigation of medical devices already approved in IMDRF countries. This would unnecessarily delay patient access to innovative medical devices, they say.

A health ministry official said he could not make any immediate comment on the device industry objections.

STENT PRICE CAP WORRIES

On another front, device manufacturers are upset that the Indian government is intending to go through with plans first announced last July to cap the prices of cardiac stents within the next 60 days.

The decision comes in response to a report by a health ministry advisory body which found "extreme overpricing" of stents. The report noted huge differences between the landed cost of the stent - which takes in manufacturing costs, shipping and customs duties - and the final cost to the patient that ranged from 294% to 1,200%.

Currently, bare metal stents are priced between INR12,000 ($179) and INR20,000 in the domestic market, while drug-eluting stents - judged to be around 1.5 times more effective than bare metal stents in lowering the number of serious adverse cardiac events, according to the report - range from INR23,000 to INR120,000, depending on product specifications.

The report suggested a "cost-effective" price of INR19,000 for bare metal stents and INR28,000 for drug-eluting stents to make the devices affordable in India, where many live on under $2 a day.

DAMPENING EFFECT?

Affordable coronary care is a key imperative for India as heart disease is the country's top killer. The country with its population of 1.25 billion is estimated to account for around 60% of the world's heart disease cases and overpricing impoverishes some families who are compelled to incur "catastrophic medical expenditure, the report found.

But the industry said the decision to include cardiac stents under the Drugs (Prices Control) Order could stop manufacturers from introducing new, technologically advanced stents into India. "The quality of products and clinical outcomes do not seem to have been given a priority," AdvaMed said.

India's National Pharmaceutical Pricing Authority is holding three days of discussions starting Jan. 4 with manufacturers, importers and chambers of commerce, doctors, public health groups and hospitals to receive input on the pricing plans.

HIGH IMPORT DUTIES

Meanwhile, there's also industry disquiet about a significant rise in import duties on medical devices, part of the Indian government's bid to boost the domestic manufacturing sector. The government has hiked import duties on medical devices and equipment virtually across the board and duties now stand at around 18.9%, according to the industry.

MTaI said some moderate duty increase might have been justified "where a high level of import substitution of an acceptable quality has been obtained or can be obtained quickly." But "this steep custom duty increase has been slapped on almost all sub-sectors/product categories of the medical technology sector irrespective of level or possibility of import substitution in the near term," said Pavan Choudary, the group's director general and managing director of device-maker Vygon India.

A more effective strategy to promote local manufacturing would be a package of incentives that includes more research and development, greater skills development, better infrastructure and improved ease in doing business, device firms said.

Major device production centers such as Ireland, Switzerland and Puerto Rico have no import duties on medical devices, noted MTaI. There's also the example of neighboring China, which is a domestic consumption and manufacturing hub, allows fast-track approval of locally produced "innovative" medical devices, and has reduced corporate tax for the sector to 15% from 25% as an officially "encouraged industry."

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COMPLIANCE CORNER:

Add These 8 Items To Your FDA Inspection Checklist

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When prepping for an FDA inspection, medical device manufacturers might fail to consider some of the more mundane yet important details – such as providing "clean" laptops for agency investigators, and making sure that opening presentations are complete and up-to-date.

Below, industry insider Steve Niedelman highlights eight points to consider that could ensure quicker, more efficient FDA inspections.

Niedelman is a familiar face in the medical device arena, working at FDA for 34 years in both its Office of Regulatory Affairs and Center for Devices and Radiological Health. He is currently lead quality systems and compliance consultant at the law firm King & Spalding.

Niedelman's comments, which came at the 11th annual FDA Inspections Summit in Bethesda, Md., were edited by *Medtech Insight* for clarity.

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1 HAVE A "CLEAN" PC AVAILABLE FOR INVESTIGATORS

"As investigators are digging more and more into electronic access of records, don't give them a PC with your enterprise system on it. Don't give them a password. Don't give them access to your complaint files unless they request it. Only give them what they request, and don't give them an opportunity to go into any emails or anything of that sort."

2 KEEP A DUPLICATE SET OF DOCUMENTS AND OTHER ITEMS PROVIDED INVESTIGATORS

"At the end of the day, if that inspection needs to be recreated as you're going through FDA-483 responses, you'll know what you provided and what the investigator request was. You could basically recreate the inspection for your benefit."

3 MAKE SURE RECORDS PROVIDED MEET THE NEEDS OF INVESTIGATORS

"Just providing investigators with paper is not going to get you anywhere. You really need to make sure that you're responsive to what that request is."

4 OFFER INVESTIGATORS AN UP-TO-DATE OPENING PRESENTATION

"Too many firms rely on, 'We created this presentation about three years ago.' They'll forget that they had an addition to their plant or revamped the way they produce something. So, make sure that your opening presentations are maintained and current to give an accurate description of what's going on at your facility."

5 INCLUDE YOUR QUALITY POLICY DURING OPENING PRESENTATIONS

"Talk about all of your procedures and policies with regard to photographs, affidavits, and all of the things that you have memorialized within your policies, so that if the investigators ask about those things, you can point to them in your quality policy. Instead of making it look like an ad hoc decision, you can show that you did make them aware of those policies during that opening presentation."

6 SHOW OFF DEVICE SAMPLES AT OPENING PRESENTATIONS

"A picture is worth a thousand words, but seeing an actual device is better. For an investigator, having a physical device in front of him or her does help explain the device and helps them better understand what you're talking about. In fact, there are firms that have cutaways of their device, so that when they talk about it, they can point to whatever part or portion of the device is being discussed. It really does help."

7 MAKE EMPLOYEES AVAILABLE FOR FDA INTERVIEWS AT TIMES OTHER THAN DURING PRODUCTION.

"FDA has a right to speak to your employees during production. But you can help them understand that interrupting an employee during whatever they're doing could result in a product recall or the manufacture of a defective product. The investigators will generally understand and wait until that employee is finished doing what they're doing to speak to them. Don't hesitate to raise that issue."

8 EMPLOYEES SHOULD BE READY TO RESPOND TO QUESTIONS ABOUT CAPAS.

"Have people who are qualified to speak to different areas of the quality system, and especially speak to different open CAPAs, or CAPAs that have been closed. Those employees talking about CAPAs need to be prepared for open-ended investigator questions. Not necessarily concrete scientific technical questions, but open-ended questions such as, 'Why did you open this CAPA?' and 'How are you doing this?' You'd be surprised at some of the open-ended investigator questions that people fall for."

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Semi-Rigid Spine Systems Will Escape PMAs, But Not Clinical Mandate

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Semi-rigid pedicle-screw systems have dodged a class III, PMA risk designation from US FDA, but will nonetheless require clinical data to remain on the US market over the long term. This formalizes an approach that has been put into place by the agency in recent years for this product class.

The agency completed its closely watched reclassification of pedicle screw devices in a Dec. 30 final order.

As anticipated, FDA has reclassified rigid pedicle screw systems, which consist of screws, rods and other components to help support fusion of the thoracic, lumbar, and sacral spine, to class II, with special controls, matching the agency's 2014 proposal. Until now, this was a class III, "preamendments" device category (meaning it existed prior to the 1976 US Medical Device Amendments), so new rigid pedicle screws have reached the market via 510(k)s for decades. The new order maintains that 510(k) requirement, but establishes more specific controls that need to be addressed related to device design, bench testing, biocompatibility and other non-clinical assessments.

There has been more suspense since the 2014 proposal on the fate of semi-rigid screw systems that employ non-metallic materials or design features, such as polymer cords, moveable screw heads, or springs, to allow for more motion or flexibility in the spine. The proposed order had labeled all spine-screw systems with these types of features as "dynamic stabilization systems" and said they would all be class III devices requiring a PMA.

This is already the accepted risk classification for non-rigid devices seeking (unsuccessfully, so far) an indication to stabilize the spine independently of a standard fusion procedure. But the proposed order would also have subjected semi-rigid systems that are adjunct to spine fusion and polyether ether ketone (PEEK) rods – which are non-metallic but, manufacturers say, rigid – to PMA requirements. That would have been a significant change from current practice.

In response, the industry cried foul, arguing that polymer-based or semi-rigid systems used in conjunction with fusion surgery are highly similar to rigid screws, with similar outcomes and adverse -vent rates, and should be in the same risk category.

FDA was generally convinced by these arguments. In the final order, the agency renamed dynamic stabilization systems that support fusion as "semi-rigid systems" (SRS), and made them class II devices, falling under the same overall "thoracolumbosacral pedicle screw system" category as the rigid systems. It also redefined the sub-category to remove the reference to "non-metallic" components as a fundamental feature of semi-rigid systems.

But makers of pedicle screw systems that meet the SRS definition will, under the final order, have to perform clinical testing, a requirement lacking for rigid systems.

"Whereas nonclinical performance testing appropriately mitigates the risks to health for rigid pedicle screw systems, nonclinical special controls are not sufficient to mitigate the risks to health, specifically, the risk of pseudarthrosis resulting in additional surgical procedures, for SRS devices," FDA states in the order. The agency also points out that some clinical testing is necessary to adequately differentiate between different SRS technologies and to predict the ability to achieve spinal fusion with a particular semi-rigid system.

While the final order took effect on Dec. 30, companies that are currently marketing a semi-rigid system will have until July 1, 2019, to submit the necessary clinical data in the form of a 510(k) amendment to keep their device on the market, the order states.

The order does not specify how many patients and how much follow up is needed to satisfy the clinical requirements for SRS devices. But the order does note, as part of its rationale for providing a 30-month transition period, that "the effectiveness endpoint of fusion for SRSs is generally assessed at one to two years post-implantation, and thus if a new study were to be initiated to collect clinical performance data, FDA would expect the 30-month period to be appropriate for SRS and allow sponsors sufficient time to enroll patients, conduct the study, and analyze the data."

Many devices on the market that would be considered in the SRS category are already subject to a clinical-data mandate from FDA. In 2009, FDA issued a so-called "Sec. 522" order for 12 device-makers to collect post-market clinical data on their 510(k)-cleared "dynamic" spine stabilization systems in response to concerns that the devices might break over time. At that time, FDA signaled that it planned to start asking for pre-market clinical data to be included in future 510(k) submissions for such systems.

Among products targeted by the 522 order are Zimmer Biomet's *Dynesys*, Paradigm Spine *DSS* and Medtronic's *CD Horizon Legacy* polymer rods.

The now-completed reclassification process for pedicle screws originated from FDA's 2009-launched "515 Program Initiative" to permanently classify all remaining pre-amendment devise. The initiative started with 26 pre-amendment product categories to address. Following the pedicle screw final order, there are two more reclassifications left to complete, both involving neurological devices.

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'Sharing' Organizations Stay In Final Post-Market Cybersecurity Guidance

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In its final post-market cybersecurity guidance published by US FDA on Dec. 27, the agency has virtually kept the language of its draft guidance the same despite some apprehension from industry groups.

The agency published a draft guidance in January that included manufacturers joining information-sharing and analysis organizations (ISAOs) that could help them pool resources and share ideas on how best to improve security on connected medical device.

FDA says it does not intend to enforce urgent reporting of a vulnerability if the manufacturer meets four requirements. Specifically, the vulnerability must not have led to a serious adverse event or death; the manufacturer must have responded to the vulnerability by notifying users and taking action to reduce the risk to a "controlled" level within 30 days; it must have provided some fix to bring the risk down to acceptable levels within 60 days; and the manufacturer must be a member of an "information-sharing analysis organization."

However, the issue of asking manufacturers to join ISAOs has been a concern to industry groups that worry about potential legal ramifications. AdvaMed had asked the agency for clarification on ISAOs, stating they should not be the only type organizations that manufacturers could join to fulfill the requirement.

Zach Rothstein, AdvaMed associate VP for technology and regulatory affairs, notes that his organization supports how FDA has provided incentives for manufacturers to participate in ISAOs.

"As stated in our Device Cybersecurity Foundational Principles, the judicious sharing of threat and vulnerability information will allow manufacturers to continually manage their device's cybersecurity throughout the product's lifecycle," he added.

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"There are many unanswered questions about ISAOs, and MITA thinks it is premature to rely on them so heavily," MITA's Megan Hayes says.

Responding to the initial draft of the guidance, the Medical Imaging & Technology Alliance (MITA) went a step further than AdvaMed and asked that ISAOs be taken out of the equation as a requirement.

Megan Hayes, director of regulatory and standards strategy at MITA, says it's not clear whether FDA's decision not to make any changes to the ISAO requirement will have any positive or negative impact on industry and other stakeholders.

"There are many unanswered questions about ISAOs, and MITA thinks it is premature to rely on them so heavily," she added.

However, Hayes is pleased that FDA removed the term "essential clinical performance" when assessing how a potential vulnerability could impact a medical device, stating it would have been confusing. In the draft version, the agency stated it was going to use the term as a standard by which the need for notifications to the agency on cybersecurity issues would be judged.

Industry, however, argued that the term essentially creates a new regulatory requirement that is already covered by established safety regulations.

"We do not think that the change in language changes the meaning of the guidance, but it does provide clarification for the reader and will reduce the potential for confusion," said Hayes.

Rothstein echoed Hayes, stating the agencies decision to replace "essential clinical performance" with may "pose a risk to health" is consistent with its request.

"This change in terminology is better aligned with existing post-market concepts, which makes the guidance clearer," he added. "Other concepts included in the draft guidance's definition of 'Essential Clinical Performance' are captured elsewhere in the final guidance."

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FDA Finalizes Post-Market Benefit-Risk Guidance

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Industry may want to use a newly final benefit-risk guidance document from US FDA to guide recall decisions, the agency said in the Dec. 27 document.

The guidance, which is part of an ongoing effort to harmonize benefit-risk considerations throughout the FDA's device center, proposes a broad framework for considering benefit-risk factors in medical device availability, compliance and enforcement decisions. It is largely unaltered from a draft version released on June 16.

FDA recommends that industry refer to the guidance to "evaluate appropriate responses to nonconforming product or regulatory compliance issues, such as determining whether to limit the availability of a medical device (e.g., a voluntary recall or market withdrawal)." In addition, the guidance says manufacturers who want to ensure FDA will consider relevant risk-benefit information should send the data to the agency.

The agency, meanwhile, may rely on the guidance to help response to device shortages, or when deciding on what action to take after a facility inspection finds compliance issues, the guidance states.

While the guidance document briefly mentions that FDA will use pilot programs and other evaluation techniques "to help determine how to apply the benefit-risk framework described" in the guidance, it doesn't discuss details such as the specific design of the pilot programs, timelines, and whether the agency plans to ask for public comment before or during the pilots.

The agency should publish any results from the pilots in an anonymized fashion so stakeholders can see how FDA plans to use the framework, according to attorney Allyson Mullen of Hyman, Phelps & McNamara. In a post on the firm's FDA Law Blog, Mullen added that the guidance might be a valuable resource for companies.

"Even if [the pilot programs do] not give industry any further information, it is clear that any company facing an enforcement action or a potentially significant product shortage situation due to a recall should contact CDRH and make as strong a case as it can for enforcement discretion based on the factors laid out in the final guidance," she wrote.

"It is clear that any company facing an enforcement action or a potentially significant product shortage situation due to a recall should contact CDRH and make as strong a case as it can for enforcement discretion based on the factors laid out in the final guidance,"attorney Allyson Mullen says.

The guidance document sports few changes from the June draft, although a few clarifying edits were made. For example, the guidance now notes that it is adopting the definitions of "serious injury and malfunction" from 21 CFR 803. And an expanded section on how the agency will assess uncertainty during risk-benefit assessments now includes an explanation of what type of real-world data may be considered, as well as possible statistical limitations the data might present.

FDA also added a fifth example to the four listed in the draft guidance. The new practice scenario discusses what actions should be taken if a pregnancy test has a high false-positive rate.

In addition to written descriptions of factors that may influence benefit-risk considerations, the guidance document includes benefit and risk assessment worksheets. The worksheets list questions that should have been asked during initial device design and testing, as well as questions needed during a post-market ("current") assessment. For example, in considering the likelihood patients will experience a benefit, the person completing the worksheet should ask, first of all, "What proportion of patients was expected to benefit from the device?" and, then, "Using real world data or other available data, what proportion of patients have been observed to benefit from the device?"

The worksheets include questions only for the post-market phase for items that aren't relevant during initial device design and testing, such as distribution of nonconforming devices or risk duration.

A third worksheet in the guidance outlines questions about the factors to consider when assessing a potential decision, such as uncertainty, mitigations, patient impact and detectability, as well as a firm's compliance history.

The document specifically targets post-market determinations. FDA finalized guidance several years ago on weighing benefit-risk factors in PMA and de novo pre-market reviews, and it issued separate draft benefit-risk guidances linked to 510(k) and investigational device exemption reviews in 2014 and 2015, respectively. Both of the draft guidances are on the device center's priority list to finalize in FY 2017.

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Multiple 'Centers of Excellence' At FDA Could Create Review Inefficiencies – Jenkins

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US FDA's cross-cutting Oncology "Center of Excellence" may be an efficient way to review new cancer treatments, but it is not a model that should be replicated for every therapeutic category across the agency, Office of New Drugs Director John Jenkins said during an exit-interview podcast ahead of his planned departure from the agency on Jan. 6.

"There is a lot of history behind how FDA is organized, and there is some rationale about how FDA is organized around products," Jenkins said. "The Oncology Center of Excellence is one model of trying to make sure that the clinical reviews of products in that area are consistent across product types. But I don't know if that's the best model for the agency for the long term."

The Oncology Center of Excellence is part of President Obama's Cancer "Moonshot" initiative, which was included in the "21st Century Cures" Act passed by Congress and signed by the president on Dec. 13. FDA moved ahead with the idea even before "Cures" gave FDA formal authorization and has been working to stand up the new oncology review structure for several months.

The intention of the Oncology Center of Excellence model is to bring together clinical review teams for drugs, biologics, devices and diagnostics under one roof, resulting in better collaboration on drug/device issues. The idea – conceived by FDA oncology review chief Richard Pazdur and advocated for by Friends of Cancer Research – originally involved centers for several different therapeutic areas (oncology, cardiology and neurodegenerative disease), but quickly became cancer-focused.

The original intent of the Centers of Excellence was that it would be a model that could be expanded to other review categories at FDA. Indeed, the "Cures" Act stipulates that FDA create "one or more Intercenter Institutes for a major disease area or areas." That language leaves open the possibility that only the Oncology Center of Excellence would be created – at least for the near-term.

Jenkins thinks a single oncology-focused Center of Excellence may be best. "I fully understand the perspective of groups out there who think it's more efficient and more effective to have all the products in a given therapeutic area reviewed in the same division or the same office." But he also believes there is value in having experts focused on certain product attributes. Devices are regulated very differently than drugs, he noted, while in biologics, gene therapies and tissues are quite different than monoclonal antibodies.

"I don't really like the idea of exceptionalism in a given therapeutic area because other therapeutic areas are important also. The patients who have diseases in those other areas deserve the same level of attention, and yet you can't create 60 different Centers of Excellence within the FDA for these smaller therapeutic areas," he said. "You've got to have a balanced portfolio of how you structure the agency."

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New FDA Web Page Aims To Clarify Position On 3D Printing

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US FDA is attempting to be more transparent with regard to one of the most complicated and difficult topics in medical device regulations by launching a new page on its website that provides sponsors resources on its thinking on 3D printing.

On the site FDA notes 3D printing encompasses regulations from its drug, biologics and device centers, and provides links. The agency also clarifies that 3D printing includes the term "additive manufacturing."

Among the resources provided by FDA is a short video starring James Coburn, a senior research engineer at CDRH, which was simultaneously posted along with the site. In the video, Coburn explains that the agency views its role as regulating, researching and acting as a resource to foster medical innovation, which includes 3D printing.

"This video was created as a brief introduction for consumers to educate them on the work the FDA does in reviewing and researching 3D-printed medical products to make sure they are safe and effective for patients and the general public," said FDA spokesperson Deborah Kotz.

She also says it was an opportunity for the agency to highlight the kinds of research it is doing in additive manufacturing that helps it understand the technology and how it may affect patient outcomes, as well as device safety and effectiveness.

While the site and video were not specifically asked for by industry, Kotz added that FDA realized it needed to do more consumer outreach to explain its role in 3D printing based on recent discussions with consumer groups at conferences and other events.

According to FDA, there are three big takeaways it has for device sponsors: the agency regulates 3D-printed devices through the same pathways as traditional medical devices; it is working with sponsors, academic institutions and others to figure out

how best to evaluate the new technology while fostering innovation; and it is continually publishing scientific articles to publicly share its research findings.

Besides the newly posted page, FDA also has a page dedicated to its Additive Manufacturing of Medical Products lab, where the agency conducts a lot of its research on 3D printing.

The added emphasis on 3D printing and FDA's attempts to be more transparent about its thinking on the topic is likely to be a welcoming development from sponsors in an industry that is seeing dramatic growth and is expected to boom in the next few years.

However, industry is still also waiting for more guidance from FDA as it grapples with potential legal issues associated with the technology. Earlier this year the agency released a draft leapfrog guidance intended to be a supplement to already existing device guidance to try help alleviate some of those concerns.

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Chronic-Care Bill Would Extend Pilot On Use Of Home-Care Devices, Promote Telehealth

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A chronic-care bill introduced earlier this month by Senate Finance Committee Chairman Orrin Hatch, R-Utah, and ranking member Ron Wyden, D-Wash., would realign Medicare payments to cover more telehealth benefits for stay-at-home patients with chronic disease.

Sens. Johnny Isakson, R.-Ga., and Mark Warner, D-Va., were co-sponsors of the "Creating High-Quality Results and Outcomes Necessary to Improve Chronic (CHRONIC) Care Act," introduced Dec. 6. The committee has been working on the bill for nearly two years. Medtronic, AdvaMed and other medical device organizations submitted extensive comments on early drafts of the legislation.

S. 3504 is targeted at providing more opportunities for chronic-care patients who are treated at home, among other goals. A discussion draft of the bill was released on Oct. 27. The bill includes a provision to extend the "Independence at Home" demonstration program for an additional two years, from its current end date of June 1, 2017, until June 1, 2019.

TELEHEALTH PROVISIONS

Telehealth provisions of the CHRONIC Care Act would permit expansion of payments for telehealth services and technology without providers having to use rebate dollars to pay for those services as a supplemental benefit. Additionally, next-generation accountable-care organization telehealth waivers could be applied to all patients, not just those in remote geographic regions.

Also, the home of the Medicare beneficiary would be considered the "originating site" for telehealth reimbursement purposes.

The bill also includes a section that would expand the use of telehealth for individuals who experience strokes by removing any originating site requirements for these beneficiaries.

EHR, REMOTE MONITORING FOR CHRONICALLY ILL

The Independence at Home program in part relies on, and reimburses the costs of, electronic health records, remote monitoring, and mobile diagnostic technology to generate and gather information about chronic-care patients to support efforts by teams of physicians, nurse practitioners and other caregivers.

Some of the goals of the chronic-care bill are also promoted in the recently enacted 21st Century Cures Act, including one "Cures" provision ensuring that individuals who quality for Medicare with end-stage renal disease may choose a Medicare Advantage plan beginning in 2021, and another updating the Medicare Advantage Risk Adjustment Model to more accurately account for individuals with multiple chronic conditions, committee members said.

Senate Finance Committee members are expected to reintroduce the chronic-care legislation in early 2017, according to Sen. Wyden.

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Puerto Rico Bolsters Its Life-Sciences Hub With R&D, Start-Up Initiatives

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Puerto Rico is on a mission to bring more life-sciences companies to the island. While the territory has been a hub for pharmaceutical and medical device manufacturing for decades, it wants to build a reputation as a go-to place for biologics contract manufacturing organizations and clinical research.

The island has taken major steps in the last year to achieve these goals. The Puerto Rico Science, Technology & Research Trust established a consortium for clinical investigation comprised of 19 sites; launched a program to accelerate startups, dubbed Parallel 18; and established a technology transfer office to commercialize discoveries from Puerto Rico's research institutions and early-stage companies.

Lucy Crespo, CEO of the trust, noted that pharmaceutical companies are moving away from small molecules and focusing on biologics. "We want to be ready to address and take advantage" of where industry is evolving, she said. The island already has a strong biologics sector with **Amgen Inc.**, **AbbVie Inc.** and **Eli Lilly & Co.** manufacturing facilities, and the trust wants to enhance this by attracting more contract manufacturing organizations.

Puerto Rico got a chance to showcase its capabilities as the host of the biotechnology conference Biolatam, held in San Juan Nov. 29-30. The event, which is intended to promote partnerships and collaborations between global companies and US, Latin American and European entities, was sponsored by EBD Group and ASEBIO, the Spanish Biotechnology Association. [**Editor's note:** *EBD Group is a company of Informa PLC, which publishes* Medtech Insight.]

One refrain throughout the meeting was the lack of recognition by the industry at large of Puerto Rico's capabilities. Elizabeth Plaza, founder and chairwoman of the regulatory and compliance consulting firm Pharma-Bio Serv, said clients often tell her, "It's a shame Puerto Rico has no more incentives," and that industry is leaving Puerto Rico. But she said that perception is inaccurate. The island replaced the tax incentives lost with the elimination of Sec. 936 of the Internal Revenue Code – which allowed companies not to pay taxes on their overseas operations until their earnings were repatriated to the US – and industry presence has grown.

However, local players still must educate would-be newcomers about what the island can offer. For example, Plaza noted that two years ago, a company came to Puerto Rico looking for investment. She met with the CEO and told him about the history of manufacturing in Puerto Rico and the company, Tampa, Fla.-based **Romark Laboratories LC**, ended up establishing a manufacturing facility in Manatí, Puerto Rico, which now produces its antidiarrheal *Alinia* (nitazoxanide).

"This case study shows the potential of the island," Plaza said. She also suggested that Puerto Rico must shift its focus from big firms to small emerging companies.

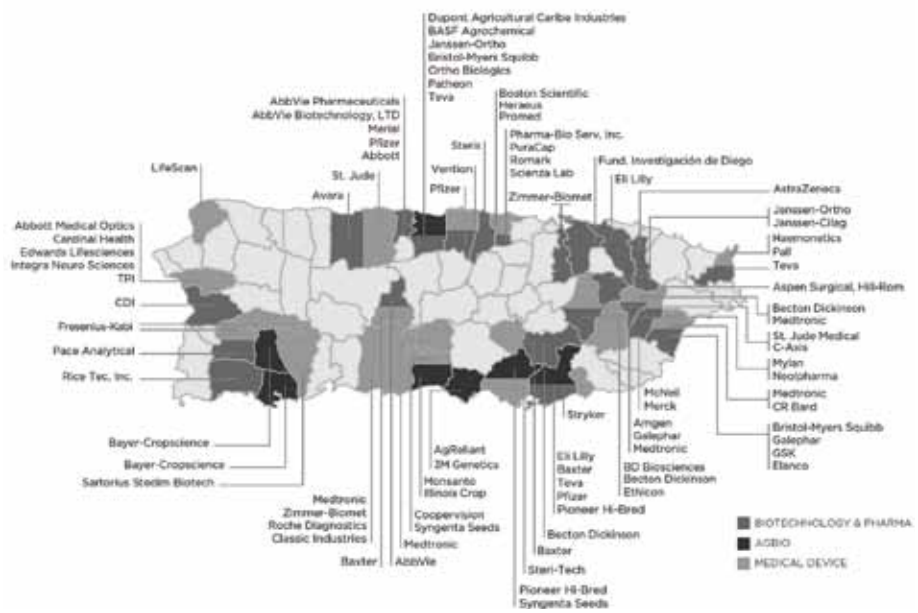
Shutterstock: PeterHermesFurian

NEW TAX INCENTIVES

The medical device industry has a significant presence in Puerto Rico. Thirteen of the world's Top 20 medical device manufacturing companies have operations there, including **Medtronic PLC**, **Baxter International Inc.**, **Becton Dickinson & Co.**, and **Stryker Corp.** (See map). The products manufactured on the island include pacemakers, implantable defibrillators, surgical instruments, dental equipment and vision correction lenses.

Victor Merced, Puerto Rico Industrial Development Company's acting director of life-sciences, described the evolution of the life-sciences sector on the island in an interview during the conference. He noted that Becton Dickinson began making thermometers on the island in 1957, but the medical device and pharmaceutical industries had their heyday in the late 1970s and early 1980s. The growth was driven by Sec. 936 of the IRS code, which was created in 1976. The tax incentive was eliminated in 1996 with a 10-year grace period for companies that remained on the island.

Life-Sciences Companies in Puerto Rico



Source: Puerto Rico Industrial Development Company

Merced said that since the end of Sec. 936 there has been a perception that companies were leaving Puerto Rico. But he said that in the last 30 years only one company, **GlaxoSmithKline PLC**, has left. Many others were swallowed up in consolidations.

"Even with the storm we are going through, Puerto Rico is still a good place to do business," Merced said, alluding to the island's financial crisis. In June, a law was enacted that created a financial oversight and management board to help the island restructure its $70bn debt.

While Sec. 936 is gone, the island has put into place several other tax incentives for life-science companies. There is a 4% corporate income tax rate for industries who perform R&D as part of their industrial activities. The corporate income tax rate is 1% when products are manufactured in Puerto Rico using novel pioneer technologies and zero percent when products are developed in Puerto Rico using novel technologies that were developed on the island.

There is also a 50% tax credit for eligible investments made in Puerto Rico, which can be transferred, sold or used against tax.

TAPPING INTO LOCAL TALENT

In addition to these incentives, Puerto Rico touts its highly skilled and educated workforce, its location as a gateway to the US and Latin America, and the fact that it operates under US laws.

The local talent was one of the reasons **Nexeon MedSystems Inc.** decided to set up an R&D division on the island. Based in Lexington, Ky., the emerging bioelectronics company is developing implantable medical devices and software platforms to support their remote management. Its lead product is an implantable neurostimulator for treatment of Parkinson's disease symptoms.

"Puerto Rico is the center of the world for pacemakers" and Nexeon uses comparable technology, Nexeon VP of Clinical Affairs Beth Rosellini explained in an interview. Rosellini and her brother, chairman and CEO Will Rosellini, moved to Puerto Rico earlier this year and plan to have 10 full-time employees on the island before the end of 2017.

"It is easier to recruit and find talent at an affordable price in Puerto Rico," Rosellini said. She noted that it is difficult for individuals with PhDs to find work on the island, so they typically go to the US to do their post doc work and often do not return.

Companies in the biopharma sector have also received assistance from Puerto Rico. In a panel on manufacturing at Biolatam, Jose Martinez, plant manager at AbbVie, noted that in 2000-2001 (when AbbVie was **Abbott Laboratories Inc.**'s branded pharmaceutical division) the firm decided to manufacture biologics on the island and that it worked with the government and the University of Puerto Rico to establish programs to prepare for that step.

Professors from the university spent several weeks at AbbVie's plant to learn what the company needed and created labs to train people about biologics. And the government spent money and resources to build a lab near the University of Puerto Rico in Mayagüez to train students as well as people working in industry.

Carola Schropp, managing director of the consulting company Hayim Group, asked Martinez if AbbVie would be willing to give projects to startups to help them get off the ground. He replied that most biotech and biopharma R&D and discovery is done in the US as scientists and resources are difficult to obtain in other places. He said the need for intellectual property and data integrity and security is also an important consideration.

AbbVie has three manufacturing plants on the island, two in Barceloneta and one in Jayuya. One of the Barceloneta facilities is a biologics plant that manufactures one product, *Humira* (adalimumab), while the other two manufacture small-molecule pharmaceuticals.

ATTRACTING CLINICAL TRIAL WORK

Puerto Rico has fallen behind other regions in conducting clinical trials and is putting a concerted effort into changing that. In a session on clinical research, Myrto Lee, director of Strategy&, part of PriceWaterhouseCooper's network, noted that there has been approximately 7% year-on-year growth in global clinical research activity. She said there has been high growth in every region but Latin America, and noted that one reason for this is probably the lack of regulatory harmonization.

Kosmas Krestos, the executive director of the Puerto Rico Consortium for Clinical Investigation, pointed to other potential factors. He noted that a lack of economic incentives on the island is driving physicians and nurses overseas. In addition, he said sponsors are often unaware of Puer-

to Rico's clinical research capabilities and qualities and have a perception that Latin American is less efficient.

But he said that the relationship between patients and doctors in Puerto Rico is very personal, which gives the island an advantage in recruiting and maintaining patients in trials.

The consortium, a network of 19 trial sites, was launched in April. Krestos said it improves the speed and quality of clinical trials and enables the research centers to compete as one and have a steady pipeline of studies.

A survey conducted by the National Science Foundation found that in fiscal year 2013, the University of Puerto Rico Medical Sciences campus and the Ponce Health Sciences University reported 4,327 clinical trials.

In other R&D activity, the Puerto Rico Science, Technology & Research Trust established the Puerto Rico Brain Trust for Tropical Diseases Research & Prevention last year. It is focused on the design of rapid diagnostic tests, vaccine development and vector control. Crespo, the Trust's CEO, said in an interview that the initial goal was to create a diagnostic for those with dengue fever and chikungunya. The Zika virus subsequently emerged and the Brain Trust focused on implementing ways to eliminate the mosquito causing the illness.

Crespo said the Brain Trust and the Consortium for Clinical Investigation provide opportunities to bring a significant number of clinical trials to Puerto Rico. The consortium's first trial was for the identification of a Zika diagnostic.

FREEING FACULTY TO PURSUE STARTUPS

In another major step to grow the life-sciences sector, the trust launched an Office of Technology Transfer in June. Its mission is to identify, protect, market and transfer the most promising research discoveries from Puerto Rico's research institutions and early-stage companies to the private sector for commercialization.

Universities in Puerto Rico were previously hindered from pursuing tech transfer by an ethics law that prohibited government employees, including professors at the University of Puerto Rico, from participating in income-generating activities, and thus blocked them from launching startups. The restriction, which was lifted in 2010, conflicted with the US Bayh-Dole Act of 1980, which permits universities to seek ownership of inventions made with federal funding.

Universities in Puerto Rico were previously hindered from pursuing tech transfer by an ethics law that prohibited government employees, including professors at the University of Puerto Rico, from participating in income-generating activities.

David Gulley, director of the technology transfer office, said Puerto Rican research institutions are far behind peer institutions in the US in disclosing inventions and funding patents. He said they are disclosing about 36% the number of inventions as their peers and spending less than $200,000 per year for patents, or about 20% of the $1.1m per year spent by peer institutions. The peers, which are institutions with about the same level of research funding, include Tufts University, Tulane University and the University of Vermont.

The research institutions in Puerto Rico consist of three campuses of the University of Puerto Rico system and four private institutions: the Ponce Health Sciences University, the two universities of the Ana G. Mendez University System, and the Universidad Central del Caribe.

Faculty of the University of Puerto Rico have begun to take advantage of the revised policy. The university's Molecular Sciences Research Center provides resources for its researchers and new start-ups.

The trust is also funding entrepreneurs outside the country. Through the Parallel 18 program, it is providing $40,000 grants to start-ups that come to Puerto Rico with the opportunity for follow-up funds if they remain. The trust received more than 900 applications from entities in more than 40 countries for the first two rounds of funding and selected 69 for the award; the third round is open for applications until the end of December. The award recipients include agriculture, medical device, information technology and engineering services companies.

BUILDING A SCIENCE CITY

The trust is now seeking to dramatically grow the island's biopharma ecosystem. It is constructing Science City, a 70-acre property in San Juan that is to house a network of research, academic and business initiatives. The mixed-use property is to include retail and living space to enable people from these sectors to live and work together. The land is within a concentration of hospitals and universities and located near the University of Puerto Rico Comprehensive Cancer Center, which opened in November.

The trust owns the property and is currently the sole tenant. The land was previously the location of the former Osco Blanco prison, which was demolished except for a few preserved pieces that are to be integrated into the design of future structures.

The road for the complex was completed at the end of November and water, electricity and fiber optics have been installed so the place is now ready for tenants.

"The full development of Science City, including the ability to do contract manufacturing here together with the establishment of a Puerto Rico vector control unit, are the major initiatives of the year," Crespo said.

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Alere Challenges Medicare Billing Block

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Alere Inc. unit **Arriva Medical LLC** is fighting the US Centers for Medicare & Medicaid's decision to ban Arriva from billing Medicare over fraud allegations.

The company appealed its suspension to a CMS administrative law judge (ALJ), who should hear the case within 30 days and issue a decision within three months, Alere says. In addition, the company asked the US District Court for the District of Columbia to force CMS to allow Arriva to stay in the competitive bidding program while the ALJ appeal is pending. The court should rule on the Dec. 28 motion around Jan. 5, Alere says.

Alere noted that Arriva was the biggest contract supplier under CMS's ongoing competitive bidding program, providing diabetic supplies to more than half a million patients. The company, which had been participating in the competitive bidding program for seven years, served about half of all participating patients.

CMS revoked Arriva's billing privileges on Nov. 4, allegedly because the company submitted 211 claims for supplies delivered to deceased patients between April 15, 2011, and April 25, 2016. But Alere said in the court case that the real reason was pressure on CMS to clear its administrative billing appeals backlog by 2020. Arriva had appealed about 250,000 claims over the last five years and was seen as a contributor to the backlog, the company says.

In addition, Alere maintains that its claims for deceased patients were largely the result of Medicare system flaws.

"We are confident that Arriva is in compliance with CMS guidelines and look forward to an expeditious and favorable outcome for both Arriva and the hundreds of thousands of patients who depend on us," the company said in a Dec. 28 press release. "The number of purported instances [of fraud] cited by CMS is *de minimis* relative to the nearly 5.8 million total claims filed by Arriva during that same period."

Arriva will keep supplying beneficiaries with diabetic supplies while the appeal is pending, the statement said.

On Dec. 7, **Abbott Laboratories Inc.** listed the Medicare billing block as one of several issues that lead the company to sue to try to back out of its January 2016 agreement to buy Alere for $5.8b. Abbott also noted that Alere had filed its 2015 annual report five months late, was hit by a major recall, and has been served two criminal subpoenas related to possible Medicare and Medicaid fraud.

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Japan's Big Imaging Players Gets NICE Boost For Virtual Chromoendoscopy

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The UK's National Institute of Health and Care Excellence (NICE) has published a draft guidance that provisionally gives the thumbs up to the use of virtual chromoendoscopy technologies – all hailing from well-known Japanese imaging companies – for assessing colorectal polyps less than 5mm during colonoscopy and determining whether they are cancerous or not.

The guidance is open for public consultation until Jan. 20.

Virtual chromoendoscopy is an electronic endoscopic imaging technique and NICE has recommended it as more "cost-effective" than histopathology, which is the current gold standard in clinical practice for diagnosing polyps.

The draft guidance recommends using Narrow Band Imaging (NBI), which is a feature of **Olympus Corp.**'s 200 series video endscopy systems; Flexible spectral Imaging Colour Enhancement (FICE), a software feature of **Fujifilm Corp.**'s endoscopy system and distributed by Aquilant Endoscopy; and i-scan, a software-based image enhancement technology manufactured by **Pentax Medical Co**. NICE's guidance states the technology should only be used if high-definition enabled virtual chromoendoscopy equipment is used and under controlled conditions. In addition, the endoscopist must be fully trained to use virtual chromoendoscopy and their performance must be audited and accredited by the joint advisory group for gastrointestinal endoscopy.

An external assessment group conducted a systematic review of the clinical effectiveness of virtual chromoendoscopy compared with a histopathology assessment of resected diminutive (<5mm) colorectal polyps. A total of 30 studies were included, with 24 studies on NBI, three studies on FICE and five studies on i-scan.

The committee looked at the differences between the three virtual chromoendoscopy and heard from clinical experts that FICE and i-scan work differently to NBI as they are software-based image enhancement technologies, whereas NBI uses optical lenses to filter light and enhance the contrast between the vessels and the surrounding mucosa.

According to NICE, the use of virtual chromoendoscopy technologies allows real-time differentiation of highly cancerous adenomas from hyperplastic polyps, which are largely benign. This differentiation could lead to fewer resections of low-risk polyps, resulting in a reduction in complications; quicker results and management decisions; and reduced resource use through fewer histopathology examinations.

Colorectal cancer is one of the most common cancers in the UK and the second most common cause of cancer death. Colorectal polyps are common, affecting 15% to 20% of the UK population.

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CONTINUED FROM PAGE 1

These indeterminate nodules present physicians with difficult choices: should they recommend invasive and risky operations? Despite best efforts, about one-third of lung nodule surgeries turn out to be negative for cancer. Should they use bronchoscopy, PET scans, fine needle aspiration? Should they do expensive and irradiating watch-and-wait repeat CTs?

This clinical problem arises all the time. A study published in November 2015 in the *American Journal of Respiratory and Critical Care Medicine* estimated 1.5 million nodules are found each year, a tenfold increase from earlier estimates. **Integrated Diagnostics Inc.** CEO Albert Luderer cites company research that estimates three million pulmonary nodules will be found in the US every year—half are found once lung cancer screening with low-dose CT is fully implemented, and half as "incidentalomas" from a scan ordered for another reason. Many of those nodules are indeterminate. The right test to sort them out could greatly improve patient care.

"If you can reduce the number of folks that don't need to go into either a wedge biopsy or a needle biopsy, you're going to have huge cost savings and huge patient benefit," Luderer says.

MARKET SIZE

Market-size numbers for this niche within lung cancer diagnostics are hard to come by. Mike Nall, CEO of liquid-biopsy company **Biocept Inc.** cites estimates of $10bn-20bn for cancer diagnostics worldwide. Today, many of those tests are for liquid biopsies engaged in tumor profiling and monitoring for patients with diagnosed lung cancer.

Summary of companies and their lung cancer diagnostic products featured in this article

COMPANY	TEST	MODALITY	STAGE	COMMENTS
Integrated Diagnostics, Inc. (Indi)	XpresysLung	Mass spectrometry measures circulating cancer-associated proteins in blood	LDT through CLIA-certified company lab	Management of indeterminate lung nodules
VisionGate	LuCED Lung Test using Cell-CT	Proprietary imaging platform for epithelial cells from sputum, distinguishing healthy from cancerous cells	Market entry planned as an LDT through a CLIA lab. Prospective FDA trial in 2017	Noninvasive. Potential to function as screening test as well as help manage indeterminate lung nodules
Genesys Biolabs	PAULA's Test	Analyzes protein biomarkers in blood, including three tumor antigens and one tumor autoantibody associated with lung cancer	LDT through CLIA-certified company lab	Early detection. Cost $118; company focused on Asian markets
Breath Diagnostics, Inc.	OneBreath	Detection of four lung cancer-specific carbonyl compounds in breath	Commencing FDA trials in 2017	Three projected indications: (1) Monitoring for recurrence post-resection (2) Evaluating indeterminate nodules (3): Early diagnosis in place of CT
Owlstone Medical	Respiration Collector for In Vitro Analysis (ReCIVA)	Detection of cancer metabolites in breath	CE marked. UK's NHS performing clinical trial	For early detection as well as management of indeterminate nodules
Veracyte	Percepta Bronchial Genomic Classifier	Genomic analysis of epithelial cells after bronchoscopy	Launched in 2015. Regional Medicare coverage anticipated in January 2017.	Management of indeterminate nodules
Chronix Biomedical	CNI Evaluation Test	Measures chromosomal instability in cell-free DNA	Test for lung cancer offered only at The London General Practice in UK. FDA treatment monitoring in 2017	Early detection
Oncimmune	*Early*CDT-Lung	Measures the presence of tumor autoantibodies in the blood	CE marked. Commercial since 2012. Undergoing clinical trials in UK	Early detection

Source: Medtech Insight

Still, available numbers regarding early detection and nodule management are impressive. The UK National Health Service estimates a savings of £245m if 10,000 lives can be saved by 2020 with early detection, a goal it's pursuing through a large study of **Owlstone Medical**'s early-detection breath test. **Oncimmune Ltd.** estimates $590m in worldwide sales in 2021 of its autoantibody early-detection test, while **Veracyte Inc.** calculates its own US opportunity alone to be $525m for its epithelial-genome test in the setting of indeterminate nodules.

Integrated Diagnostics, which uses mass spectrometry in its indeterminate-nodule assessment test, is even more optimistic. "This is one of the few blockbuster markets that are out there in diagnostic medicine," Luderer says. Assuming $3,000 per test for three quarters of a million indeterminate nodules per year, "it is potentially a $2bn market" in the US.

BREATH TESTS FOR EARLY DETECTION

Owlstone Medical is leading the charge on breath analysis for early detection of lung cancer with the 3,000-patient LuCID study (Lung Cancer Indicator Detection) underway at 21 sites in the UK. The company's CE-marked *ReCIVA* test collects volatile organic compounds (VOCs) from the patient's breath in a proprietary collection device, then analyzes them for evidence of early cancer with its microchip sensor technology called *FAIMS* (Field Asymmetric Ion Mobility Spectrometer). The LuCID study is collecting data to determine ReCIVA's sensitivity and specificity.

In the race to develop a breath test, Owlstone had a key advantage: its parent company Owlstone Inc. originally built FAIMS to sniff out chemicals for military and security applications with $71m in funds. The company then reprogrammed its software to detect different chemicals for lung cancer, spinning out Owlstone Medical in March 2016. England's National Health Service has funded the LuCID trial with £1.1m.

With an anticipated commercial release in 2017, the company is still working on regulatory approval, including in the UK and Europe.

Louisville, Kentucky-based **Breath Diagnostics, Inc.** is working on a breath-based strategy as well. Michael Bousamra, a Kentucky-based thoracic surgeon, co-founded the company in 2014, joined by University of Louisville chemical engineer Xiao-An Fu, who developed the company's technology. *OneBreath* uses mass spectrometry to measure concentrations of four carbonyl compounds in a single breath—compounds that not only rise in the setting of lung cancer but also fall or even normalize again after treatment, a discovery Bousamra and Fu published in *Annals of Thoracic Surgery* in October 2016.

Though the ultimate aim is to replace CT as a screen for high-risk patients, the company hopes to first come to market as an CT adjunct for monitoring after cancer resection, with positive breath markers suggesting the need for a PET scan. Bousamra, who is also company president, is writing a grant for US FDA enabling studies, with hopes of commencing in January 2018.

> "This is one of the few blockbuster markets that are out there in diagnostic medicine. Assuming $3,000 per test for three quarters of a million indeterminate nodules per year, it is potentially a $2bn market in the US."
> - Albert Luderer, Integrated Diagnostics, Inc.

A second proposed indication is to develop OneBreath as an FDA-approved means of evaluating indeterminate lung nodules on CT. A study published in September 2014's *Journal of Thoracic and Cardiovascular Surgery* found that OneBreath outperformed PET scans for determining the malignancy of indeterminate pulmonary nodules.

"Especially in the Ohio River Valley, where histoplasmosis and other fungal etiologies are common, we have a lot of false positives on PET," Bousamra says. "Our specificity was 77% and the PET scan specificity was 39%." The company plans a multi-center pilot study for that indication."

Bousamra's aim is to partner with a mass spectrometry company. "They're our natural strategic partners in this business," he says. "Breath analysis is a brave new world where [mass spec] companies are interested in expanding."

CHROMOSOMAL INSTABILITY FOR EARLY DETECTION

San Jose-based **Chronix Biomedical** technology's laboratory uses next-generation sequencing to analyze chromosomal instability of cfDNA in plasma, primarily to help direct medical procedures in patients with positive mammograms or elevated PSAs. But the company also offers a lung-cancer screening test to look for chromosomal gains and losses in ctDNA in high-risk smokers, generating a result called the copy number instability score (CNI). At present, the 2000 GBP screening test is offered only at London General Practice to help doctors decide whether to send certain high-risk smokers to imaging. The plan is to take a version of the test, Delta Dots, through a 510(k) FDA pathway in H1 2017. (Delta Dots predicts treatment outcomes after the first cycle of therapy.)

IMMUNOLOGICAL APPROACHES

Oncimmune Ltd. has been commercializing its immunoassay blood test, *EarlyCDT-*

Lung, in the US since 2012. Its panel of tumor antigens allows for detection of circulating autoantibodies against tumor cells in the bloodstream, a signal that can rise for years before the cancer becomes symptomatic.

"We compliment CT by identifying a very high-risk group that will be suitable for CT screening. We can reduce tenfold the number of CTs to be done on patients," says CEO Geoffrey Hamilton-Fairley.

As such, EarlyCDT-Lung is being tested as a pre-CT screening test in the UK. The NHS is currently conducting a trial of 12,210 high-risk patients to evaluate the test's accuracy; those who test positive for tumor autoantibodies then receive LDCT screening.

Interim data presented at December's World Conference on Lung Cancer in Vienna, Austria showed that of 599 patients with positive test results, 16 had lung cancer, with 12 of those in an early stage. Final study results with two years' CT follow-up will appear in 2019. EarlyCDT-Lung's specificity is 93%. A future application of the test could be evaluation of indeterminate nodules, while a next-generation technology will allow healthy people to "bank" their autoantibody "fingerprint" in order to serve as their own control in a future test. The company plans to complete validation for the latter next year.

US Medicare part B reimburses at $124 for EarlyCDT-Lung. Total 2021 sales are projected to be $590m globally, including $275m in the US; these figures assume inclusion of a planned kit form of the test to be rolled out in H2 2017 (CE mark of the kit is anticipated in H1 2017). The company has 14 US distributors in place for its CLIA-certified Kansas lab.

A business unit of Rockville, Maryland-based 20/20 Gene Systems, **Genesys Biolabs** has a non-small cell lung cancer early-detection test on the market. *PAULA's Test* is a laboratory-developed test (LDT) offered through primary care physicians for asymptomatic people aged 50 or older, who have smoked at least a pack a day for 20 years or longer. The company's Maryland CLIA-certified lab analyzes a blood sample using a panel of biomarkers comprising three tumor antigens and one autoantibody. It then runs the results through a proprietary algorithm that takes some clinical factors into account and stratifies the patient into higher or lower-risk categories, offering guidance as to whether the patient should receive LDCT screening. Genesys reports that PAULA's Test has a sensitivity of 74% with a specificity of 80% in the target population; about 99.3% of patients rated low-risk will indeed be cancer-free, while about 8.3% of high-risk patients will actually have cancer. A planned 2017 rollout of a next-generation test will have higher sensitivity and specificity, according to director of sales Barry Cohen.

Retailing at $118 plus shipping and handling, the test is not generally covered by US insurance companies, and Genesys plans to eventually convert to an FDA-approved kit model in the US. Cohen says the company is highly oriented to the Asian market: "We have found it to be much more receptive to our approach." The venture arm of Chinese insurance giant Ping An Insurance (Group) Company of China, Ltd., holds a seat on the company's board. Genesys also estimates a $3bn market in East Asian countries for a cloud-based consumer app to track annual cancer screening results, as biomarker screening is a widespread practice there, according to Cohen.

Genesys estimates a $3bn market in East Asian countries for a cloud-based consumer app to track annual cancer screening results, as biomarker screening is a widespread practice there.

The company's next funding round, aimed at up to $21m, is anticipated to be a Series B or small IPO to close in February 2017, with half of investors likely from East Asia.

PROTEOMICS FOR NODULES

Much as the PSA test seeks a single protein that may indicate prostate cancer, **Integrated Diagnostics (Indi)** offers a blood-based proteomic molecular diagnostic that detects multiple cancer-associated proteins. *Xpresys Lung* is a diagnostic adjunct to CT, identifying lung nodules likely to be benign to prevent an unnecessary workup. The company sees a $2bn US market in early lung cancer diagnosis.

Indi was founded in 2009 as a spinoff from the laboratory of Lee Hood, who was also founder of Amgen and Applied Biosystems.

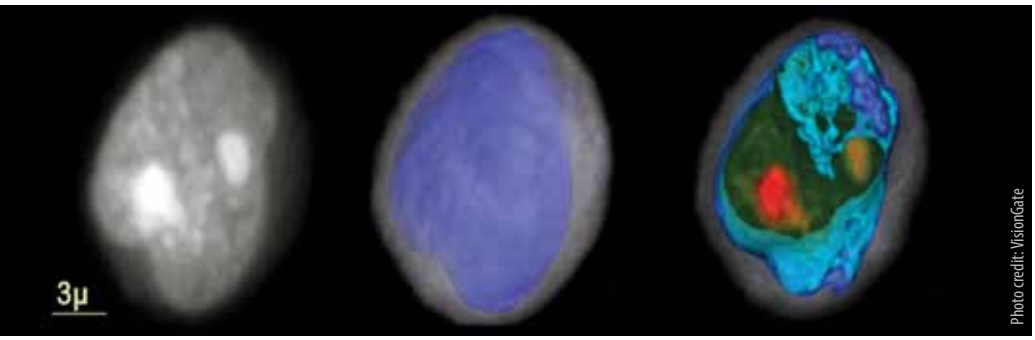
Xpresys Lung, performed in Indi's CAP- and CLIA-accredited lab in Washington State, uses a technology Hood helped pioneer called multiple reaction monitoring mass spectrometry (MRM). This technique allows analysis of the proteome—hundreds of expressed proteins at a time—to find patterns betraying the presence of cancer.

In November 2015, a prospective multicenter study of 475 patients reported in *Lung* that the test may reduce by one-third the number of indeterminate nodules that go to surgery and are benign. A larger prospective multicenter study of patients with indeterminate nodules, including one-year CT follow-up, will be submitted for publication soon.

CEO and director Albert Luderer says that based on trial results, Indi is developing a second-generation test that uses just two protein analytes (down from 11 in the first test), and incorporates five clinical risk factors into the predictive model for lung nodules that are benign.

Indi is in talks with MolDx, a program of CMS contractor Palmetto GBA that evaluates molecular diagnostic tests for possible coverage and reimbursement. If a favorable determination is made, the company will launch a C round of financing (it raised $80m in previous rounds) to take Xpresys Lung through to commercialization, including establishing a registry and conducting an interventional clinical utility study. The goal is to launch to the public by the end of 2017.

VisionGate's LuCED test



Cell-CT creates 3-D tomographic images of cells in coughed up sputum

EXAMINING CELLS TO UNDERSTAND NODULES

If you could see a lung epithelial cell and knew what to look for, you could tell by its appearance whether it was cancerous. Phoenix, Ariz.-based **VisionGate's** *LuCED* test uses a noninvasive sputum sample and proprietary technology to do just that. Called *Cell-CT,* the platform creates 3-D tomographic images of cells coughed up in sputum. These images are so detailed that the cells' morphology can be categorized according to 704 structural biomarkers; cancerous cells differ enough from healthy ones that they can be detected based on these morphologic differences.

In a nine-site study presented at WCLC in Vienna in December, LuCED was used to examine sputum samples from 60 high-risk but cancer-free people, and 79 with biopsy-confirmed cancers. The technology found the cancers with 90% sensitivity and 97% specificity.

The company is writing pre-submission documents and aims to begin FDA prospective trials in H2 2017, first studying the use of the technology for incidental nodules. Chief medical officer Javier Zulueta says the technology may in future also prove useful as an adjunct to LDCT screening to reduce false positives, and even in pre-LDCT screening for lung cancer. Though the company hasn't priced LuCED, "our intent is to be cost-effective with LDCT," says company president Scarlett Spring.

VisionGate was founded in 2001 by its current CEO Alan Nelson, a bioengineer with numerous patents and publications. Trinnovate Ventures, a unit of Blue Cross Blue Shield of Arizona, led a March 2016 $20m funding round, one the company plans to close by the end of this year.

Because Cell-CT can detect dysplastic (precancerous) as well as cancerous cells, VisionGate is exploring its potential role in the chemoprevention of lung cancer. It has a licensing agreement with the University of Colorado Cancer Center for the drug iloprost, which Center research with bronchoscopy has shown can reverse dysplasia. The use of noninvasive LuCED to monitor the preventive effects of iloprost is currently in Phase 2 trials.

Faced with an indeterminate nodule, some pulmonologists opt to perform a bronchoscopy. But sometimes bronchoscopy results, too, are unclear. **Veracyte's** *Percepta Bronchial Genomic Classifier* collects lung epithelial cells from the mainstem bronchus during diagnostic bronchoscopy, then, in the face of an indeterminate bronchoscopy result, analyzes those cells to detect genomic changes, some of which suggest the presence of lung cancer.

"There are about 300,000 of these bronchoscopy procedures done today on patients with a nodule that's being worked up for lung cancer. We believe that number is going to continue to grow," says CEO Bonnie Anderson, "Unfortunately, if the bronchoscopy does not confirm cancer, it cannot rule cancer out. The false-negative rate can be quite high. That is where Percepta comes in."

Anderson added that the test does not require that physicians give up any elements of their diagnostic routine. "We're not taking anything out of their hands that they're using today—we're enhancing it," she says. "This is very fundamental to getting diagnostics accepted, adopted, and paid for."

The company puts Percepta's US market opportunity at up to $525m.

Headquartered in the Bay Area, Veracyte made its name with *Afirma*, a widely-covered test allowing for evaluation of thyroid nodules, and went public in 2013. It launched Percepta in April 2015 as a laboratory-developed test. The technology is based on a principle called field of injury, in which cells distant from a tumor may still display telltale genomic alterations.

A July 2015 *New England Journal of Medicine* paper reporting on two prospective studies of Percepta, AEGIS I and AEGIS II, reported a negative predictive value of 91% and when combined with bronchoscopy led to a cancer-detection sensitivity of 97%, compared to 75% sensitivity for bronchoscopy alone. Findings from an ongoing multicenter clinical utility study were reported at the October meeting of CHEST in Los Angeles; these included reduction by about one-third of invasive procedures in patients with a low or intermediate risk of lung cancer before their Percepta test.

In fall 2016, the company announced that multiple Medicare contractors had is-

sued draft local coverage determinations for Percepta, which, after its likely finalization in January, will allow Medicare coverage for the test for nearly two-thirds of US Medicare beneficiaries.

In 2017, Anderson says, Veracyte plans to expand access to Percepta by stepping up marketing efforts. The company's hope is for Percepta to be added to guidelines, becoming part of the standard of care. "We believe being able to remove 30% of invasive procedures when we have only been on the market a year and just now started to get coverage, is a really good early indication that the test should be successful," she says.

MAJOR CHALLENGES FOR DIAGNOSTICS

No matter how promising their products, companies looking to commercialize early diagnostic tests face an unusually steep road.

"Why is this market under pressure? It takes a fantastic amount of money to be able to do this, and then the coverage decisions are not always predictable," says Integrated Diagnostics CEO Luderer. "You've got to commit early to clinical trials when you just don't know what the outcome's going to be. So it's very risky."

Demonstrating that a screening test works requires clinical trials with huge numbers of patients, as the large-scale NHS studies of Oncimmune and Owlstone demonstrate. And in the US, at least, what diagnostic companies lack in regulatory headaches they may make up for in reimbursement struggles.

That's in part because most of their tests are laboratory-developed tests, which don't require FDA approval and are CLIA-regulated instead.

> Veracyte puts the US market opportunity for its Percepta Bronchial Genomic Classifier at up to $525m.

Not being FDA-regulated means no established codes and no guaranteed reimbursement. From a payor's point of view, it can be difficult to untangle which diagnostics will be truly informative and which won't, says Michael Liang, a **Baird Capital** partner and Integrated Diagnostics investor. Increasingly, payors want to see a test show up in clinical guidelines before they'll cover it—but the time and money it takes to make it into guidelines can break a company.

"It takes so much work in terms of money and cost and time to get these coverage decisions, and even when you've done it right, the payors are slow to respond and give you the coverage," Liang says. "It's been the biggest factor that has been limiting the industry."

In October 2014, the FDA released a draft guidance document laying out its intention to bring LDTs under its regulatory aegis, but on Nov. 18, 2016, the agency announced it would delay the release of final guidance. Though some insiders dreaded the prospect of FDA regulation, others say they wouldn't object and have designed their clinical trials to an FDA level of rigor.

Still, various mixtures of optimism, confidence in non-US markets, and a conviction that lung cancer patients deserve better is driving these companies forward. Insiders say there's room for several good products in this space, and some believe the right tests could transform lung cancer care in a few years' time.

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START-UP SPOTLIGHT:

Apama Medical, Targeting AFib With An RF-Balloon Combo

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The goal of a new atrial fibrillation (AF) catheter ablation system from **Apama Medical Inc.** is to bridge the gap that exists today between point-by-point ablation and cryoballoon ablation.

The standard and historic solution for treating AF is to use a radiofrequency (RF)-irrigated catheter with an electrode tip that can move from point to point for ablation, along with three-dimensional electroanatomical mapping for guidance. Treatment for patients with paroxysmal AF (intermittent AF) involves creating a circle around the pulmonary veins to isolate the erratic electrical activity. However, patients with persistent AF (constant AF) often require additional ablations in other areas of the atrium, besides the pulmonary veins.

While point-by-point ablation provides precise targeted therapy and is versatile in that it can adjust to various anatomies and be used in both paroxysmal and persistent patients, "the procedure is long as it can last up to six hours, and is technically challenging," says Apama CEO Amr Salahieh. Thus, point-by-point ablation is limited to a select group of skilled electrophysiologists (EPs), and often only one procedure can be performed each day.

As a result, cryoballoon ablation has been growing rapidly. This newer technique entails inflating a balloon against the pulmonary vein, and then delivering nitrous oxide to cool the tissue to a frozen state. "After ablating two or three times, the EP moves on to the next pulmonary vein," Salahieh notes.

Compared to point-by-point ablation, cryoballoon ablation reduces the skill level needed by an EP to perform AF ablation, and has the ability to treat more patients per day than is possible with a point-by-point ablation system, according to Salahieh.

However, the downside of cryoballoon ablation is that "it is a one-size fits all approach," Salahieh says. "You can turn on the whole balloon all at once, but you are unable to turn on only a portion of the balloon, so it is not targeted therapy. In essence, it is all or none." In addition, cryoballoon can only be used to isolate the pulmonary veins, so it is limited in its ability to treat persistent AF.

Apama RF Balloon Catheter

Source: Apama Medical, Inc.

The Apama RF balloon catheter system, on the other hand, incorporates the best features of point-by-point ablation and cryoballoon ablation. The multielectrode, RF balloon catheter enables one-shot, customizable ablation geometries. Further, it has built-in cameras that enable real-time visualization of electrode contact.

"Our system has the efficiency of cryoballoon ablation because it can apply one-shot ablations, combined with the versatility and the sophistication of point-by-point ablation because the EP can fine-tune lesions by selecting the specific ablation pattern based on real-time visualization of electrode contact," Salahieh explains.

Initially, Apama Medical is focusing on treating paroxysmal AF, but ultimately plans on treating those with persistent disease as well, since the system can create other lesion patterns beyond pulmonary vein isolation (PVI). Currently, the EP catheter ablation market constitutes about 950,000 procedures annually worldwide, for a yearly market cap of about $4bn.

CE mark for the Apama RF balloon catheter system is expected in 2018, followed by premarket in 2020.

Salahieh, who is principal founder of Apama, was previously co-founder and CEO of Sadra Medical Inc. (percutaneous aortic valve replacement), which started in 2003. Many years later, "I was looking for another area in cardiovascular where I could make significant impact on patient outcomes," he recalls. "The only area that I could identify that really needed better technology was AF. At the time, the average success rate was only about 60%, causing many patients to have two or three treatments."

Salahieh and his team aspired to create a level playing field in AF, so that most EPs could achieve the same results as the most experienced EPs. "However, we did not want to come up with a completely different procedure," Salahieh says. "We wanted to provide EPs with the tools needed to perform the procedure they wanted to do, but do it easier, faster and more reliably, so that more physicians can have good results and treat more patients."

From the beginning, Salahieh and his associates were committed to develop-

ing a balloon-based approach, due to its ease of use and one-shot approach. "We thought that by placing multiple electrodes on the balloon, our system would do the job," Salahieh says. They discovered, though, through animal studies, that the system could not reliably and consistently verify contact with tissue, making it challenging to determine which electrodes to turn on for ablation.

"We were unsure if we should ablate with all the electrodes or some of the electrodes, and what power setting to use, despite its versatility," Salahieh explains.

The developers decided that the only way they could solve this dilemma in a definitive manner was to use cameras to show the EP exactly what was going on at the interface of the balloon and the tissue.

Apama Medical has 17 issued and 61 pending patents. Salahieh declined, however, to divulge if the company is sharing any royalties and/or revenues with another entity.

As an entrepreneur, Salahieh was principal founder and CEO of **Maya Medical Inc.** (renal denervation) in 2010, which was sold two years later to **Covidien**. **Sadra Medical** was also acquired, by **Boston Scientific Corporation**, in 2011. Moreover, Salahieh was principal founder of **Kalila Medical Inc.** (a steerable sheath for heart intervention) in 2010, which was sold to Abbott Laboratories in 2016.

The Apama RF balloon catheter system has three components: a balloon, a sheath, and an RF generator. After the EP performs a transseptal puncture to access the left side of the heart, the sheath is placed across the puncture. The balloon then slides in the sheath and a guidewire slides inside a pulmonary vein. Next, the balloon is inflated and positioned against the vein, and appropriate electrodes are selected based on real-time visualization from the built-in cameras.

The ablation is then turned on. Afterward, the EP verifies that the electrical signals from the balloon have been diminished using the integrated sensing electrodes on the catheter, which eliminate the need for an additional mapping catheter. This process is repeated until all appropriate pulmonary veins have been isolated.

The entire in-patient procedure under general anesthesia or conscious sedation takes on average 90 minutes, which compares favorably to second-generation cryoballoon procedure times.

The training of EPs who already treat AF patients with a balloon takes a few days, according to Salahieh.

Since April 2016, a total of 17 AF patients have been treated with Apama's device. "All of these patients have exceeded our expectations," Salahieh reports. "The treatment procedure time was shorter than we anticipated, given the early stage of our development. The outcomes have also been good so far, comparable to second-generation balloon systems."

Besides cryoballoon ablation from **Medtronic** (*Arctic Front*), Apama Medical has three other major competitors. **CardioFocus Inc.** (*HeartLight*) is a laser balloon that is limited to treting paroxysmal AF.

VytronUS Inc. uses low-intensity collimated ultrasound (*LICU*) to ablate. "However, unlike RF, which is well understood and has a good safety record, ultrasound is a newer modality for creating lesions in the heart and more data is need for universal acceptance," Salahieh conveys.

As with Apama, **Johnson & Johnson** is also developing an RF multielectrode balloon. "But that solution relies on monopolar ablation versus bipolar ablation, and does not use built-in cameras," Salahieh states.

European sales of the device are expected to begin in 2018, with an unknown type of sales force at this time, but the procedure is reimbursable.

The $36m raised to date represents three rounds of financing: a Series A round of $4.7m, led by Broadview Ventures, which closed August 2013; a Series B in the amount of $17.9m, led by Ascension Ventures, which concluded January 2015; and a Series C of $13.2m, led by Medvance Incubator Partners, which closed in November. Over the past four years, Apama has also received two grants from the National Science Foundation (NSF) Small Business Innovation Research (SBIR) program. The company does not plan on any new fundraising in the near-term.

Apama, reflecting other start-ups in the cardiovascular space, is likely an eventual attractive takeover candidate by a major EP player, as it continues expanding the number of treated patients. The major suitors would be **Biosense Webster Inc.**, **Medtronic PLC**, Boston Scientific, **St. Jude Medical Inc./Abbott** and **AtriCure Inc.**

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Contact: Amr Salahieh, CEO

Industry Segment: Electrophysiology

Business: Multielectrode, radiofrequency balloon system features single shot, customized ablation geometrics and built-in cameras

Founded: May 2009

Founder: Amr Salahieh

Employees: 38

Financing To Date: $36m

Investors: Ascension Ventures; Medvance Incubator Partners; Broadview Ventures; ONSET Ventures; Incept LLC; Angel Investors

Board of Directors: Fred Khosravi (Incept); Tara Butler (Ascension Ventures); Greg Casciaro (Cardiac Dimensions Inc.); Henry Chen (Delos Capital); Rob Kuhling (ONSET Ventures); Amr Salahieh; Motasim Sirhan (Elixir Medical Corp.)

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