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Liquid Biopsy In Oncology: An Increasingly Crowded Landscape

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The ability to diagnose a tumor and monitor its progression and response to treatment without the need to obtain a tissue biopsy has been a long-standing goal of cancer management. This capability is now in hand thanks to the technology known as liquid biopsy, currently one of the most exciting sectors of the *in vitro* diagnostics market.

The term 'liquid biopsy' is used to refer to a noninvasive diagnostic test that can identify various types of cancer or other

conditions by detecting biomarkers in fluid samples such as blood or urine, obviating the need to obtain a tissue biopsy. This approach is being pioneered by several companies and is expected to bring multiple benefits, not least the fact that such tests are relatively quick and easy to perform and are far less invasive than tissue biopsy.

Although the main target of efforts to develop liquid biopsy products up to now has been cancer, the technology also has

other potential applications, such as prenatal diagnosis of chromosome abnormalities via a blood sample or monitoring chronic kidney disease via urinary proteome analysis.

FOUR DISTINCT CANCER APPLICATIONS

In a recent report on liquid biopsy, analysts at financial services company JP Morgan noted that although the technology is still in the early stages of development and adoption, it has the potential to be a powerful tool in guiding physicians to the most appropriate course of therapy for any given patient.

The analysts envisage four distinct applications for the technology. Closest to realization is probably its use in theranostics, as a companion diagnostic to guide targeted therapeutics. By 2020, this market could be worth \$2bn a year, they say. Within two to three years from now, liquid biopsy technology will also come to be used for predicting the likely course and outcome of disease for individual patients, the analysts believe, a market that could be worth an additional \$4-7bn by 2020. (See Figure 1.)

A little further in the future, the JP Morgan analysts believe that liquid biopsy will increasingly be used for monitoring therapy, particularly for tracking drug-resistant mutations and quantifying the response to treatment. This segment could be worth an additional \$5bn by the

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(via video conference)



Scott Huennekens



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PMA efficiency

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FDA continues to improve its overall efficiency in reviewing new-device PMAs, while 510(k) performance remains flat, according to *Medtech Insight's* August US approvals analysis.

EU regulation recap

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In the latest *Medtech Insight* article detailing chapters of the pending EU Medical Device and IVD Regulations, we explore provisions addressing notified bodies.

Pacts and partnerships

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A new bi-monthly round-up of key medtech industry alliances and collaborations tracked by *Strategic Transactions*.

Fresenius eyes Indian poll position

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The largest global dialysis services provider bought India's second-largest dialysis chain with the aim of expanding in a country where end-stage kidney disease incidence is skyrocketing.

Device Week

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Our weekly podcast, where *Medtech Insight* journalists discuss topics they are covering that impact the device and diagnostics sector.

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inside:

Cover / Liquid Biopsy In Oncology: An Increasingly Crowded

Landscape – Liquid biopsies – carrying out diagnostic tests on liquid samples such as blood or urine rather than on tissue biopsy material – appear ready to revolutionize the management of cancer patients. This article marks out who's who in the increasingly busy landscape and the key technologies that are showing promise.

EDITORS' PICKS

- 5 Danaher Buys Cepheid For \$4bn, Citing Molecular Diagnostics Strength** – Danaher is paying a 54% premium to acquire Cepheid, the maker of the fully automated GeneXpert rapid genetic testing system. Danaher executives cited Cepheid's large installed base and potential for growth and efficiency improvements as justifications for the deal.
- 6 Injunction Stops Sales Of Qiagen GeneReader** – The system was launched late last year, but a preliminary injunction issued by a federal court in California will now block Qiagen from marketing its GeneReader sequencing system in the US. Illumina had filed a patent claim against the system, and the court found that the claim is likely to succeed.
- 7 Medtechs Must Forearm For Russia's Tough Market-Access Pathway** – Russia has the most complex medical device registration process in the world – that's the claim of one senior medtech regulatory expert speaking at a recent Informa Life Sciences conference. Local knowledge and local partners will be key elements for those companies wishing to succeed in Russia.

POLICY & REGULATION

- 9 Korea Moves To Halt Reuse Of Disposable Devices Amid HCV Outbreak** – South Korean measures to root out the reuse of disposable medical devices amid a local outbreak of hepatitis C may have a positive impact on the industry, but the government still has some barriers to cross as industry participants are calling for more comprehensive measures.
- 10 \$30m In Device User Fees Will Go To Real-World Evidence Evaluation System** – US FDA will be able to tap \$30m in user fees over a five-year span to support an independent coordinating center for collection of real-world evidence under its nascent NEST program, according to device center Director Jeff Shuren.

Medtech insight

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11 FDA Reattempts Guidance On Third-Party 510(k) Review Program – The US agency is again attempting to outline its thinking on the 510(k) third-party review program in a new draft guidance. The program, which allows accredited organizations to conduct 510(k) reviews for certain products, has had a lackluster performance since it was first mandated by Congress in 1997.

12 Six-Year Study Will Compare Bayer's Essure With Tubal Ligation – US FDA has accepted a post-approval study plan by Bayer HealthCare for its Essure permanent sterilization device, which is under intense scrutiny in response to adverse events and charges of clinical trial misconduct. The protocol entails a non-randomized, six-year cohort study comparing Essure-implanted women to tubal ligation sterilization subjects.

13 UDI Extensions: Convenience Kits, Repackaged Devices, Combo Products – Just a little more than two weeks before the next Unique Device Identification compliance date, US FDA has granted two-year extensions to three product categories that raise particular complications for UDI labeling.

COMPANIES

14 St. Jude Hacking-Risk Allegations: US FDA Continues Assessment, As Firm Files Lawsuit – While conflicting reports have surfaced regarding the veracity of allegations from a short-seller that a significant number of St. Jude cardiac rhythm management devices have serious cybersecurity flaws, FDA says plans to complete an initial assessment of the allegations soon. The Minnesota device-maker, meanwhile, says it is suing the short-seller for disseminating false information.

15 Abbott, Alere Agree To Mediation For Troubled Merger – Abbott announced plans to purchase Alere in January, but the merger has so far been delayed by, Alere alleges, Abbott's foot-dragging. Abbott, meanwhile, points to federal investigations that have delayed Alere's financial filings.

COMMERCIAL

16 VC Deals Analysis: How Four Bad Months Can Spoil The Barrel – Another slow month for VC financing deals means the total deal value for 2016 to date is now lagging behind that for the same period last year.

R&D

18 Pulmonx Reaches Multiple Milestones In Lung-Valve, Diagnostics Development – Encouraging results from the IMPACT study of Pulmonx's Zephyr endobronchial valve in patients with homogenous emphysema – a population with almost no other options – is the latest in a string of good news for the Silicon Valley company, which wants to create a new paradigm of personalized device therapy for pulmonary disease.

Danaher Buys Cepheid For \$4bn, Citing Molecular Diagnostics Strength

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Diversified scientific and industrial instrument conglomerate **Danaher Corp.** will add **Cepheid** to its stable of diagnostics companies following a \$4bn acquisition, announced Sept. 6.

Both companies' boards have agreed that Danaher will acquire all of Cepheid's outstanding shares for \$53 per share, a 54% premium over Cepheid's closing price of \$34.42 on the last business day before the deal was announced. The \$4bn total also includes debt and acquired cash. The companies expect to close the deal by around the end of this year, subject to approval of shareholders and other customary closing conditions.

Danaher will finance the acquisition with its available cash plus issuance of new debt. It estimates the Cepheid acquisition to be moderately dilutive to its net earnings per share and approximately \$0.05 accretive to non-GAAP, adjusted diluted net earnings per share in the first full year after the acquisition. By the fifth full year post-acquisition, Cepheid will be approximately \$0.30 accretive to Danaher's non-GAAP, adjusted diluted net earnings per share, according to Danaher.

Danaher holds more than 20 operating companies in the environmental, dental, industrial technology, and life-sciences sectors. In 2015, the Washington, DC-based company reported \$20.5bn in sales, and about 40% of that was from diagnostics and life-sciences products, including chemistry systems, immunoassay systems, hematology and flow cytometry products, microbiology systems, and laboratory workflow solutions. Its diagnostics brands include **Aperio, Beckman Coulter, Leica, Mammotome, HemoCue, Surgipath, Iris,** and **Radiometer Medical.**

Cepheid claims the largest global installed base of molecular diagnostics instruments and the broadest menu of tests, led by its fully automated *GeneXpert* systems for rapid genetic testing platform that can usually return results in less than 90

“While the deal is questionable from a valuation perspective, we believe Cepheid checks most of the boxes of an attractive Danaher target,” Jefferies analyst Brandon Couillard says.

minutes. The Silicon Valley-based company generated \$539m in revenue in 2015, with double-digit year-over-year organic revenue growth. During the Sept. 6 earnings call announcing the acquisition agreement, Danaher executives pointed out that about 75% of Cepheid's revenues come from recurring “razor/razorblade” sales, which fits with the type of businesses Danaher has been acquiring over the past two decades.

TWO-WAY BENEFITS

During the earnings call, Danaher CEO Thomas Patrick Joyce emphasized how Cepheid's leading position in molecular diagnostics complements Danaher's strengths in other areas of diagnostics.

“While there are many other molecular platforms on the market, what we find so compelling about Cepheid's [GeneXpert] platform is its simplicity [and] its rapid time-to-result,” Joyce said. He also cited GeneXpert's ability to accommodate more than 20 tests without any need to adjust the instrument, and its capacity to scale to any lab's requirements as major advantages of Cepheid's technology over other molecular testing platforms.

“Cepheid represents a strategically important addition to Danaher's existing diagnostic businesses,” he said. “Specifically, Cepheid will significantly accelerate our presence in molecular diagnostics” and complement Danaher's Beckman Coulter *Veris* high-volume molecular system to create a more comprehensive system for customers. “Our existing diagnostics businesses will benefit from Cepheid's exceptional assay development capability, improved

access to underpenetrated segments like smaller and medium-sized hospitals, as well as the high-growth point-of-care and oncology testing markets.”

Cepheid's products will benefit from being sold alongside Danaher's broad line of other diagnostics products by Danaher's international 3,000-person sales force, which “already has well-established infrastructure and deep market visibility in high-growth markets, including China.” Joyce also talked up the potential for Danaher to boost Cepheid's operational efficiency and profitability by implementing what it calls the Danaher Business System, an ongoing program of efficiency improvement processes and measurement tools based on “lean” manufacturing principles. Danaher says DBS has evolved from a collection of manufacturing improvement tools in the 1980's into a philosophy and set of values that drive growth and efficiency across all of its companies.

Joyce noted that Cepheid has recently implemented several manufacturing cost-efficiency initiatives, but the application of DBS can drive those efficiency gains even further. Danaher CFO Daniel Comas added that Cepheid's gross margins are currently around 50%, but “we would expect that would be much higher, probably north of 55% in time and maybe even higher, particularly as the consumable business gets to be even a bigger piece of the overall pie,” he said. Danaher has already identified about \$100m in cost synergies and another \$100m in annual revenue synergies that it expects to realize in the first five years of integrating Cepheid.

GOOD FIT, BUT TOO EXPENSIVE?

Commenting on the Danaher-Cepheid deal in a Sept. 6 note, Jefferies analyst Brandon Couillard wrote: "As a leader in clinical molecular diagnostics, Cepheid fills an obvious hole in Danaher's diagnostics franchise around molecular, which it struggled to develop internally, that will complement its existing presence in other adjacent verticals, including core labs (Beckman Coulter), critical care/point-of-care (Radiometer), tissue/histopathology (Leica Bio) & microbiology (Siemens)."

However, Couillard believes the cost of the acquisition leaves Danaher with less

capital-deployment flexibility in the near term. He forecasts that, if the companies can achieve their projected \$100m of cost synergies and \$100m of revenue synergies, the deal will increase Danaher's earnings per share by 6% by 2021, but generate a return on invested capital of only about 7%. "As one of the last remaining well-capitalized pure-play traditional hospital-based diagnostic assets with a large existing installed base, the price tag clearly puts a premium on Cepheid's scarcity value."

Couillard estimates that Cepheid currently has an installed base of about 11,000 GeneXpert systems, so the price of the ac-

quisition works out to an enterprise value of about \$375,000 per instrument and compares favorably to a median of \$535,000 per instrument for other established high-growth diagnostics assets historically.

"While the deal is questionable from a valuation perspective, we believe Cepheid checks most of the boxes of an attractive Danaher target: leading brand, high-gross margins, high-recurring revenues, room for margin expansion/operational efficiencies with DBS, and macro-growth drivers," Couillard concludes. ▶

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Injunction Stops Sales Of Qiagen GeneReader

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A California district court has granted **Illumina Inc.**'s request for a preliminary injunction blocking **Qiagen NV** from distributing its *GeneReader* next-generation sequencing instrument in the US as part of ongoing patent litigation.

The Sept. 9 injunction was triggered by an Illumina suit filed in June that alleges the GeneReader violates Illumina's U.S. Patent No. 7,566,537, which covers a way to sequence DNA via synthesizing.

The lawsuit is part of a series of patent disputes stretching back to 2012, when **Columbia University** and **Intelligent Bio-Systems Inc.**, which licensed Columbia's technology, sued Illumina for patent violation. Illumina countersued, saying Columbia and IBS had violated Illumina's '537 patent. Qiagen purchased IBS in 2012.

Qiagen and Illumina then dropped the case and sent their dispute to the US Patent & Trademark Advisory Board for *inter partes* review. PTAB ruled that several claims in Columbia's patent were invalid, but upheld the '537 patent while declining to launch a review. Illumina filed the current case shortly after PTAB made its final decision.

Judge William Alsup granted the injunction because he believed the court is likely to find Illumina's patent valid, the injunction states. While Qiagen said the patent is invalid due to obviousness, Alsup found Qiagen's evidence on the point weak. For example, a technical document that Qiagen said could have led scientists to discover the patented technique only applies to one of the seven challenged claims in the '537 patent.

"Although Qiagen's invalidity arguments are not frivolous, this order finds that Illumina is likely to defeat them, particularly in light of Qiagen's burden to prove invalidity with clear and convincing evidence," Alsup wrote. "Thus, this order finds Illumina is likely to succeed on the merits and now turns to the equitable considerations for a preliminary injunction."

Further, Alsup found that Qiagen's attempts to introduce the GeneReader to the US could cause "irreparable harm" to Illumina. Qiagen is using a non-standard business model in which labs



may rent the GeneReader and pay per use, while Illumina sells its units outright. This and the fact labs rarely replace sequencing equipment could give Qiagen an unfair advantage without the injunction, Alsup said.

"At this crucial inflection point in the development of the market for DNA sequencing equipment for clinical laboratories, Illumina would suffer irreparable harm if Qiagen were allowed to capture and define the market with pirated technology alongside its pre-existing relationships and disruptive business mode," Alsup wrote.

Qiagen was disappointed by the court's ruling, company CEO Peer Schatz said in a statement. "We believe our intellectual property position in next-generation sequencing is strong, and we are pursuing all legal means to get the current decision reviewed by the U.S. Court of Appeals for the Federal Circuit as soon as possible," he added.

The company is trying to speed the development of an upgrade to the component involved in the patent litigation so the GeneReader can return to commercial sales in the US with comparable or improved performance, said Schatz. Qiagen does not expect the court's decision to affect its financial forecasts, which didn't include any significant anticipated GeneReader sales; the system was only introduced in the US in December 2015.

A trial in the case is set for November 2017. ▶

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Medtechs Must Forearm For Russia's Tough Market-Access Pathway

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Medical device manufacturers working in the Russian market may need to be both patient and ever-alert as the relatively new risk-based national regulatory system, which is based on a resolution (Resolution 1416) that became effective at the beginning of 2013 and continues to expand.

At the same time, local and foreign players must keep an eye on developments within the evolving Eurasian Economic Union (EAEU), where the aim is to establish a single market that applies across member-states. In the device world, the intention is that the EAEU will in time replace the member-states' national systems. However, that day will not come as soon as some officials might hope. Indeed, some sort of delay seems likely, according to Russian industry insider Alexey Stepanov.

Stepanov was among regulatory experts speaking at the Informa Life Sciences (ILS) conference in Brussels, Belgium, in June.

More recently, Stepanov used his blog (*Medical Device Regulations in Russia and Eurasian Union*) to point to another area where there is a delay in the regulatory system reforms, specifically related to Resolution 1517, which addresses state regulation of prices for implantable medical products.

IMPLANTABLES HICCUP

On Aug. 1, 2016, the Russian government published a new resolution (735) that deferred by one year the deadlines for manufacturers to provide the pricing documents that are necessary to develop reference prices for implantable devices. This list of reimbursable implantable devices will be drawn up by Roszdravnadzor, the Federal Service for Surveillance in Healthcare.

The newly set Resolution 735 deadlines are July 15, 2017, for the registration of the maximum sale prices for implantable



devices, and Sept. 1, 2017, for the establishment by the regional authorities of maximum wholesale mark-ups on the actual selling prices of the implantables. The Russian Ministry of Health has also given itself until Oct. 1, 2017, to agree on the procedures for re-registering maximum sale prices.

Originally, the prices were to have been set by July 15, 2016, senior medtech regulatory expert Georg Bauer told ILS conference delegates. Bauer, who is head of the medical and health services foreign affairs department for notified body and certification firm TÜV SÜD Product Service GmbH, explained that the idea behind Resolution 1517 was that manufacturers can participate in public tenders only if their price does not exceed the maximum price on a list of products. But the mechanism is not yet clear, he said.

Bauer went further, opining that Russia "is the most complex medical device registration process in the world." It is a system that requires patience, and something that does not help matters is

that Roszdravnadzor does not engage in any form of oral consultation with applicants: correspondence and requests can only be made in writing.

KEY PLAYERS IN RUSSIAN REGULATION

Bauer also imparted useful advice to players in the Russian market during his ILS presentation. In Russia, Roszdravnadzor is the key medtech regulatory player, responsible for registrations and the technical regulatory service. The agency does not handle cosmetics, pharma products or consumer devices.

Then there are the expert organizations, which assess the technical data for device files and decide whether the manufacturer can proceed with a registration.

Other key players are the local legal representatives and authorized representatives (ARs), which manage the local-level registration process and are responsible for post-market surveillance. Bauer noted that these can be distributors, importers, other third-parties or a

locally based group subsidiary. They act as the interface between Roszdravnadzor and the manufacturer. Local representatives must have a contract to manufacture and must have power of attorney from the manufacturer to establish their responsibilities and rights.

Bauer stressed that it is vital that distributors and ARs are given a full brief by the manufacturer of what the product is, including which components and accessories are covered, and what (and whose name, importer or manufacturer) should be on the registration certificate. Given that registration certificates are now of unlimited validity in Russia, "there might be problems later on if this is not accurate," Bauer warned.

RISK-BASED SYSTEM

Resolution 1416 sets out the minimum requirements for the conformity assessment process, and indeed the whole registration process. Registrations are risk-based, using classes I, IIa, IIb and III, and the system is similar to the risk-based classification in the EU Medical Devices Directive (MDD, 93/42 EC). But there may be classification differences, where, say, an EU class I product could be class IIa in Russia to class IIa, based on Resolution 1416.

The Russian approval process can be divided into four stages. The first two are mandatory – covering the registration process, and the declaration of conformity (DoC). For the DoC, only the address of a company established and registered in Russia can be used. DoCs are valid for three years. Stages three and four of the approval process are for active medical devices and those that incorporate a measuring function.

The first stage of device registration covers the technical, electromagnetic compatibility (EMC) and toxicology and biocompatibility tests to be performed. The relevant documentation is then forwarded to the expert organizations, which inform Roszdravnadzor if they can be accepted.

There are 10-12 labs in the Moscow area that can perform different types of device testing. The Russian-language

website at www.fsa.gov.ru can be used to check accreditations.

Class I products generally can employ a simplified regulatory route in which new clinical evaluation and testing is not necessary as long as existing clinical and scientific data are submitted. For all other classes, the manufacturer needs to seek Roszdravnadzor approval to perform the necessary clinical evaluation. The results are assessed by an expert organization, which notifies Roszdravnadzor. If there are no hitches, the agency issues a certificate of registration and the company is informed.

Bauer observed that an overseas applicant may also need to show evidence of the home-market evaluation, as well as ISO 13485 certification, and brochures and technical information.

Fellow ILS conference speaker Anton Dulov, of the Russian device registration consulting agency STM LLC, noted that *in vitro* diagnostics are in class III, as they are perceived to present risks to public health. He also commented that while registering a device in Russia is supposed to be a nine-month process, in practice, it often runs for a year or longer.

The most common reason for file rejection at this stage is the submission by the manufacturer of several devices that cannot be grouped together in a single registration filing, Stepanov observed.

CLINICAL EVALUATIONS

Bauer highlighted two routes to complying with Russian clinical evaluation requirements. The more common approach is to rely on scientific literature and data analysis combined with a discussion of achieved in clinical studies performed outside of Russia. Less frequently, manufacturers may have to perform new clinical studies in Russia, particularly if the device is new or complicated, or if previous results have not been sufficient.

If a trial involves human subjects, manufacturers must obtain a statement from the ethics commission and perform trials in specifically authorized hospitals (specified in a Russian-only listing). Bauer noted that it is possible to track the reg-

istration progress process online. A new guidance – a "how-to" on clinical and technical aspects – is now under review and can be expected to be published soon to replace the current version, dated November 2013. There is expected to be an opportunity for stakeholders to submit comments.

Elsewhere, all device certificates issued prior to 2013 have to be reissued by the end of this year. There is a 30-day reissue process that has to be initiated by the company and must be accompanied by fees.

The DoC has replaced the Russian GOST-R certificates, which are now voluntary. But some clients still use them for marketing reasons, as they are still often referred to.

FINAL THOUGHTS

Time, money and patience are needed to successfully navigate the Russian regulatory system, said Bauer. He stressed that a good local partner who has native experiences in Russia is invaluable.

He advised communicating with the Russian authorities in the Russian language. And he stressed the need to plan early, as he said that even for class I devices more and more requirements are being introduced and more questions are being asked.

The class I process has purportedly been simplified, but with the hurdles seemingly rising ever higher, some companies might even be dissuaded from participating in the Russian market, some experts suggest.

For Bauer, there is almost no "black-and-white" in Russian medtech regulation, and it is becoming harder to secure registrations. The increase in questions might be perceived as an attempt to slow down the process. The West's sanction against Russia don't help, of course. But against this, there is a big private clinic market in Russia. The clearest and most obvious take-home for device companies from regulatory experts is the value of having a native Russian speaker in the organization. ▶

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Korea Moves To Halt Reuse Of Disposable Devices Amid HCV Outbreak

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In a new policy move aimed at preventing the potentially dangerous reuse of disposable devices, South Korea plans to introduce a medical device distribution information system that can systematically manage the import, manufacture, distribution and use of medical devices.

The latest step is a part of broader measures to prevent and manage a series of local outbreaks of hepatitis C at local clinics that was found to have been linked to reused syringes.

The new system aims to help prevent reuse of disposable devices by confirming their distribution and usage volume, and the Ministry of Health and Welfare plans to submit a revision to Medical Device Act reflecting such changes by the end of this year.

HCV OUTBREAK

From late 2015 to early 2016, more than 500 people tested positive with the hepatitis C virus (HCV) and more than 20,000 patients at three South Korean clinics are under epidemiological investigation.

The reuse of syringes is believed to be the main cause of the mass outbreak, said the health ministry, which added that the mass outbreak stemmed from “lack of awareness in risk of hepatitis C and false practices” by some physicians.

As there is no vaccine for the disease, it is important to identify patients in the early stages and prevent further infections. However, it is difficult to identify patients early as 70% of those in the acute phase are asymptomatic, and South Koreans also have a low recognition of the disease. South Korea is estimated to have about 300,000 hepatitis C patients.

NEW CONTROLS, TESTS

Although details of the new system haven't been outlined yet, domestic medical device industry executives expect it to have a positive impact on the sector by increasing sales of disposable devices. But they urged the government to come up with comprehensive measures taking into consideration views from all relevant sides, rather than being pushed into releasing patchy steps.

“We will be able to find out if disposable devices are reused or not, so usage volume could increase,” said an industry official. “But this may also mean that device-makers will need to put more effort into quality control as management becomes more transparent.”

As part of the latest measures to prevent and manage HCV, the government will also seek to include a test in the national standard medical check-up, continue to expand national health insurance coverage of hepatitis C drugs, and toughen punishment of “immoral” medical practices. All medical institutions that come across hepatitis C patients will also be obliged to report the cases.

Meanwhile, some medical industry participants are reportedly calling for the government to improve the current loss-making price structure of materials for medical treatment, including



Reused syringes blamed for recent South Korean hep C outbreak

disposable syringes, which appear to be the reason behind unethical reuse practices by some physicians.

“Medical insurance cost isn't properly reflected for the majority of medical devices,” said the industry source.

But as different government ministries oversee the distribution and safety of medical devices, it will be difficult for a single ministry to carry out this measure. Instead, the proposal will have to go through “discussions among medical institutions, doctors, the Ministry of Food and Drug Safety, Health Insurance Review & Assessment Service and the health ministry” to reflect their views, said another industry official.

TIME FOR UDI?

The official added that it is also time for South Korea to introduce a system like the US FDA's Unique Device Identification (UDI), which would be beneficial to both the industry and patients.

The domestic medical device sector has been calling for a system that can effectively distribute and track medical devices, and the recent outbreak of hepatitis C has fanned such need.

The UDI system aims to adequately identify medical devices through their distribution and use. Among its benefits, it allows more accurate reporting, reviewing and analyzing of adverse event reports so that problematic devices can be identified and corrected more quickly.

In fact, a South Korean ruling party lawmaker held a policy seminar earlier this year to discuss the introduction of such system to South Korea.

Following the HCV outbreak, the government already unveiled some measures earlier this year to root out the reuse of disposable syringes, including creating a reporting center and conducting on the ground inspections.

In May, the Medical Service Act was revised to include an obligation not to reuse disposable syringes, and violations could lead to the revocation or suspension of licenses to practise.

In other moves, in April South Korea decided to reimburse **Gilead Sciences Inc.**'s blockbuster HCV drugs *Sovaldi* (sofosbuvir) and *Harvoni* (ledipasvir/sofosbuvir), sharply lowering the cost burden of patients. ▶

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\$30m In Device User Fees Will Go To Real-World Evidence Evaluation System

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FDA will get \$30m in device industry user fees over five years to help fund broader use of real-world evidence for devices in the US.

The agency and industry negotiators announced a draft MDUFA IV agreement last month, which will form the basis of the user-free program that stretches from fiscal years 2018 through 2022. The agreement includes support for a pilot program of the FDA-championed National Evaluation System for health Technology (NEST) program, envisioned as a collaborative effort for vetting, validating, and employing registries and databases to continuously assess device safety and performance.

FDA device center Director Jeff Shuren disclosed more details of the user-fee agreement with regard to NEST, including the \$30m figure, during a Sept. 6 briefing to the Alliance for a Stronger FDA in Washington, DC.

"We, in a very short time, are going to announce selection of a [NEST] coordinating center. For the very first time I can tell you there will be funding to support the coordination center, \$30 million in user fees over the five years of this MDUFA [span] to get it up and running, and to start investing in pilots on accessing it," Shuren said.

Industry negotiators seemed initially skeptical to the idea of funding NEST idea with user fees because of fears that collection of real-world evidence such as registry and clinical trial data on medical technology products would not significantly accelerate device innovation. But FDA has pushed hard for RWE, even releasing a draft guidance in late July on

how it plans to rely upon that real world data in evaluating product submissions, and industry ultimately agreed that their user-fee dollars could support at least a pilot version.

Both Shuren and FDA Commissioner Robert Califf are enthusiastic about using the dollars for the coordinating center, which will be the focal point for NEST activities such as sharing clinical trial and registry data among device product sponsors. The agency officials argue this will lower the data-generation costs for supporting PMA, *de novo* and 510(k) submissions. The purpose of the center is to drive down the time and costs – as well as increasing the value and use of – real-world data "through a market-driven, collective buying-power approach," Shuren told the Alliance group, which lobbies Congress for higher funding levels for the agency, among other activities.

The agency will award a \$3 million grant to the coordinating center in the upcoming year, and also plans to award \$1 million for additional pilot programs to collect real-world data.



NEST will have to prove itself," Shuren says.
"If you demonstrate return on investment, then people will use it."

DATA-USE AGREEMENTS

Among the agency's recent accomplishments in support of RWE data collection, Shuren said FDA is establishing data-use agreements with 14 registries to allow access to a total of 22 million patient records "and more agreements such as these are in the works," he told the Alliance.

The "value proposition" of such agreements is that they can allow device manufacturers to provide high-quality evidence in less time and at lower cost than it would take for one firm to run a clinical trial on a device under development. The evidence can be used to support pre-market approval and clearance in addition to supporting payer coverage and reimbursement, the CDRH director noted.

However, the success of FDA's move to RWE collection and to reliance upon NEST itself requires a demonstrated return on investment, Shuren cautioned.

"NEST will have to prove itself," he acknowledged. "If you demonstrate return on investment, then people will use it." ▶

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FDA Reattempts Guidance On Third-Party 510(k) Review Program

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FDA is making a renewed effort to issue guidance addressing the long-languishing 510(k) third-party review program. The agency has put out a second attempt at a draft guidance to modernize and globally harmonize the program after a first-attempt draft was issued in 2013.

Enacted in the FDA Modernization Act of 1997, the third-party review program, which allows accredited organizations to conduct 510(k) reviews for certain products, was intended to make the 510(k) program more efficient, but over the ensuing almost 20 years, demand for third-party 510(k) reviews from companies has been low.

The new draft follows the lead of the 2013 version but has been expanded considerably (from eight pages to 34 pages). The document attempts to harmonize concepts established by the International Medical Device Regulators Forum (IMDRF) for the recently launched Medical Device Single Audit Program (MDSAP), which employs accredited third parties to perform facility inspections, for the third-party 510(k) review program.

Furthermore, the draft delves into how third parties can review 510(k)s, its requirements and recognition and re-recognition of third-party review organizations, the content and format of third-party review organization applications for initial recognition and re-recognition, and the agency's thinking on when to suspend or withdraw recognition of such organizations.

The issuance of the expanded draft guidance may be a first step in a new effort to rekindle the program so it can meet its initial expectations. Last month, FDA and industry inked a draft agreement for the next user-fee round (MDUFA IV, which will stretch from FY 2018 to 2022) that includes an agency commitment to revive the third-party 510(k) program.

According to details from the final user-fee negotiation meeting, FDA plans to begin a training and audit program for third-party reviewer organizations and to publish performance reports. In addition, the agency says it intends to seek authority from Congress to expand the scope of the program to eliminate the requirement for routine re-review by FDA of third-party 510(k) reviews, which is considered one of the current inefficiencies of the program.

Under the program third-party review organizations may review 510(k) applications but are limited from reviewing class III devices and class II devices that are permanent implants, or considered life sustaining or life-supporting. They are also not able to review combination products that require multi-center review or consultation.

The draft guidance details the process organizations could use to apply for third party review organization designation including sending FDA copies of their initial recognition application. After acknowledging receipt of the application via email, the agency says it will give a decision to the organization within 60 days.

While such review organizations are not obligated to participate in FDA pre-submission meetings with sponsors, the agency encourages them to be involved in such meetings if the sponsor consents.

"The [Third Party] Review Program is intended to enable FDA to focus its internal scientific review resources on higher-risk and complex devices, while maintaining a high degree of confidence in the review of low-to-moderate risk and less complex devices by TP Review Organizations, and to provide manufacturers of eligible devices a voluntary alternative review process that may yield more rapid 510(k) decisions from FDA," the guidance states.

While device-makers are not obligated to use third-party reviewers, those that do become eligible for a 30-day response from the agency as stipulated under the Food, Drug and Cosmetics Act.

FDA notes in the draft guidance that, at minimum, third-party review organizations have to follow certain criteria: they may not be employed by the federal government; they may not be owned or controlled by a medical device manufacturer, supplier, or vendor; and they may not design, manufacture, promote, or sell such devices. The agency says the third-party review organizations should communicate in English and that non-English speaking organizations should designate one English-speaking officer to be a liaison to the agency. ▶

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Six-Year Study Will Compare Bayer's Essure With Tubal Ligation

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US FDA plans to continue its review of **Bayer HealthCare LLC's** high-profile *Essure* permanent sterilization device via a six-year long, 2,800-woman, comparative post-approval study.

The study will last six years, but while it is ongoing, "If we see any new evidence that will cause us to change our position, we'll go ahead and do that. But it will be driven by the science," FDA's device center director Jeff Shuren explained at a Sept. 6 event in Washington, DC.

FDA disclosed the plans for the post-market study in a Sept. 2 update of its regulatory activities surrounding the *Essure* device.

Shuren, speaking at a general update session sponsored by the Alliance for a Stronger FDA, added that the agency, in reviewing Bayer's study plan, had been careful to consider patient input. The agency received thousands of written comments before and after a well-attended September 2015 Obstetrics and Gynecology Devices Advisory panel meeting that was convened in response to problems that women reported with *Essure*.

Essure first went on the market in 2002 after FDA approved a PMA submitted by the device's original sponsor, **Conceptus Inc.** It was marketed as a less invasive alternative to tubal ligation sterilization to women who had made a decision to stop bearing children. The product works by stimulating scar tissue to form in the fallopian tubes – blocking egg passage – through the implantation of tiny metallic coils into the tubes that are inserted with a special tool via the vaginal canal.

But major complaints from women about adverse events associated with the *Essure* inserts gradually escalated over a 10-13 year period so that by the time of the 2015 advisory panel meeting, FDA had received more than 5,000 reports of adverse events.

More than 40 individuals testified during the public hearing of crippling pain, irregular bleeding, allergic and hypersensitivity

Any change in FDA's position to keep *Essure* on the market, despite intense patient pressure to remove it, "will be driven by the science," insists device chief Jeff Shuren.

reactions, as well as insert migration, and ectopic and unwanted pregnancies they experienced after the *Essure* devices were implanted in their fallopian tubes.

"Everything has its tradeoffs," Shuren commented Sept. 6. "And what you see as part of our policy is being very clear about what we understand are the risks with the technology, and also making sure those are being discussed with women."

In addition to ordering Bayer to conduct a post-market surveillance study, FDA intends to require the company to place a boxed warning and "Patient Decision Checklist" for physicians to discuss and share with patients on the *Essure* package labeling "to help ensure that a woman receives and understand[s] information regarding the risks and benefits of the device," FDA states.

REMOVAL SURGERIES AMONG MAIN ENDPOINTS

Under the study plan, Bayer will recruit subjects between 21 and 45 years of age who have not been pregnant in the prior six weeks, comparing those who chose to undergo hysteroscopic sterilization with *Essure* to those who received laparoscopic tubal sterilization. The study population could also include some 18-21 year olds, according to Bayer's general study protocol parameters.

The main study endpoints will include:

- Chronic lower abdominal and/or pelvic pain;
- Abnormal uterine bleeding (new onset or worsening)

- Hypersensitivity and allergic reactions, and autoimmune disorders; and
- Invasive gynecology surgery, including *Essure* insert removal.

Among the secondary study endpoints will be other adverse events and results of bloodwork, pathology, histology and metallurgic testing if the device is removed, as appropriate. During the 2015 panel meeting, some panelists discussed the need for more nickel sensitivity testing for prospective *Essure* patients, due to the device's nickel content. Bayer also will examine the effectiveness rate of the device; i.e., how many women actually get pregnant after using *Essure*.

Bayer has promised extensive follow-up visits as part of its study plan – particularly at the 36-month mark. The company, beginning with March 30, 2017, is obligated to report back to FDA on its study results on *Essure* and the trial's progress every six months until Sept. 2, 2018. After that, the company must report to the agency on a yearly basis through Sept. 1, 2023.

FDA STILL REVIEWING CITIZEN'S PETITION

The agency also mentioned in its update that it is in the process of "completing its evaluation of the trade complaint about clinical trial misconduct, notably that medical records from trial participants were altered to reflect more favorable data about participants' experiences."

The "trade complaint" came in the form of a Citizen Petition filed by plaintiff's at-

torney firm **Koch Parafinczuk & Wolf, P.A.** last year. Bayer has said that it “disagrees” with the allegations in the petition, and that many of the complaints in the filing address alleged practices by the prior Essure sponsor, Conceptus.

The Citizen Petition was labeled a trade complaint by FDA, and continues to be investigated as such, the agency said.

PRESSURE FROM CAPITOL HILL

The agency promised in late February 2016 to have the sponsor, Bayer, perform a post-market study of the sterilization device, and the device center’s chief scientist, William Maisel, stated at that time, “We believe Essure should remain an available option for women seeking permanent birth control who are adequately informed of the risks.”

But at least two congressional members were upset enough with the agency’s decision to keep Essure on the market that on June 8, they introduced a pair of bills, “Ariel Grace’s Law,” (H.R. 5303), and the “Medical Device Guardians Act,” (H.R. 5404), in part to help address women’s grievances about Essure.

Reps. Mike Fitzpatrick, R-Pa., and Louise Slaughter, D-NY., cosponsored H.R. 5403 to remove the federal preemption defense for PMA devices like Essure that patients claim have caused them harm, and H.R. 5303, which would mandate that physicians report adverse events like those seen with Essure patients directly to FDA, or to the agency’s MAUDE adverse events database. Problems with a second FDA-cleared device (power morcellators) that patients have complained about were cited by the two congressional members as part of the reasoning behind their introduction of H.R. 5404.

But Shuren reinforced the benefits/risks tradeoff with Essure during the Sept. 6 “Alliance for a Stronger FDA” meeting, commenting that FDA is trying to review the product “in a responsible manner.”

“For some women, it will be the right decision [to use Essure]; for some women, it will not be the right decision to use it,” he remarked. “But let patients and practitioners make that decision – and just be armed with the knowledge we have.” ▶

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UDI EXTENSIONS: Convenience Kits, Repackaged Devices, Combo Products

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The next big Unique Device Identification compliance date in the US is coming fast, but some specific types of products just got an extra two years of cushion.

Sept. 24 is the deadline for companies to put UDIs and link the information to the Global Unique Device Identification Database (GUDID) for remaining class II devices (lifesaving and life-sustaining class II devices needed to comply last year). And many companies may be struggling to make that date, according to *Medtech Insight* reporting.

Just a little more than two weeks from the date, FDA decided to give a two-year extension to some product categories that might be running into particular complications. On Sept. 6, the agency disclosed it would give manufacturers of three types of products until Sept. 24, 2018, to comply with the UDI and GUDID requirements. Those are:

- **Convenience kits:** FDA issued a draft guidance in January that seeks to define the UDI rule’s “convenience kit” exception for individual device UDI labeling when devices are packaged together for the convenience of the

user. The draft proposes to remove some types of surgical kits from this exception, but while FDA works to finalize the guidance, manufacturers will get until next year to comply.

- **Repacked single-use devices:** Individual single-use devices, other than implants, that are all of a single version or model are not required to bear a UDI provided they are distributed together in a single device package, according to FDA. If the devices are repackaged, they will require a UDI, but now the agency is giving repackagers of such devices an extra year to comply with that mandate.

- **Devices co-packaged or cross-labeled with drugs:** FDA is also giving an extra year for UDI compliance to devices that are either co-packaged with or cross-labeled to a drug or biologic as part of a combination product that is regulated by the agency’s drug or biologic centers.

FDA makes clear that the extensions do not apply to implantable, life-sustaining or life-supporting devices. ▶

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St. Jude Hacking-Risk Allegations: US FDA Continues Assessment, As Firm Files Lawsuit

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US FDA says it continues to investigate allegations by investment research firm that **St. Jude Medical Inc.** cardiac devices are particularly vulnerable to hacking and should be recalled. The agency plans to complete an initial internal assessment in the next few weeks and will disclose its findings publicly if warranted.

Meanwhile, St. Jude has filed a lawsuit against Muddy Waters Research, which issued the report late last month purportedly demonstrating that they were able to conduct hacks of the firm's devices, causing them to "crash" and draining them of their battery strength, and risking to harm or kill patients if not dealt with.

The demos were conducted with cybersecurity research firm MedSec Holdings Ltd. and were disclosed in conjunction with Muddy Waters taking a "short" position on St. Jude's stock, meaning it will gain financially if the firm's share price declines. St. Jude vigorously denies the veracity of Muddy Waters' claims.

Since the report was released, FDA, as well as independent researchers, have made an effort to determine whether there is anything to the report that St. Jude's devices are markedly more vulnerable than competitor products. But so far there has been no definitive answer.

FDA says it is still working with Homeland Security's Industrial Control Systems Cyber Emergency Response Team (ICS-CERT) to assess the claims.

Suzanne Schwartz, FDA's top officer on issues of medical device cybersecurity, said in an interview that the agency was notified by Muddy Waters about its findings at the same time the report was issued publicly. While not speaking directly about the Muddy Waters report, Schwartz, the director of Emergency Preparedness/Operations and Medical Countermeasures at CDRH, emphasized that in line with the agency's recent draft guidance on post-market cybersecurity, FDA encourages those who find potential

The much anticipated acquisition of St. Jude by Abbott is still expected to go through later this year.

cybersecurity flaws in medical devices to first discuss the matter with the manufacturers to try to find a solution.

Schwartz said FDA is open to speaking with researchers about their concerns but the preferred process is for them to first reach out to the manufacturers.

"Ideally, that is where we seek to move the entire medical device ecosystem, where a vulnerability identifier, a reporter, goes directly to the device manufacturer to provide that information so the appropriate kind of assessment and vulnerability ... can be determined," Schwartz said.

If there is no potential harm to patient safety, ideally the agency would not have to be involved and the manufacturer could mitigate the issue on its own. However, if there is serious concern for patient health, ICS-CERT assigns the case a tag and directs the researcher to work with the manufacturer and government. At that point, the draft guidance suggests that a 30-day clock starts up for the manufacturer to provide an initial assessment of the allegations, though FDA makes clear that is not currently a requirement.

"When there is an alleged statement regarding a vulnerability that has the potential for devastating consequences, then certainly as would be the case with any risk regarding a medical device or medical product, that type of evaluation and response gets escalated," Schwartz said. "And it is our mission and responsibility to inform the public of ... the appropriate steps that should be taken in a timely manner"

Schwartz says FDA was able to put out an alert on **Hospira Inc.**'s *Symbiq* infusion pump last year within weeks of finding out from a hacker named Billy Rios that

the product had a serious cybersecurity vulnerability. She also notes while the agency may come out with an initial assessment on such allegations, its assessment is subject to change over time as new information becomes available.

BENEFITS OUTWEIGH RISKS?

FDA is not the only third-party organization looking into the matter. Several reports and analysis have tried to clear up the ongoing dispute between Muddy Waters and St. Jude Medical but despite their efforts, it seems there is still no simple answer.

Following Muddy Waters' report, researchers at the University of Michigan conducted their own analysis of the findings and concluded that there were holes in the investment firm's analysis.

The university researchers say they reproduced the same error messages cited by Muddy Waters as evidence of a successful "crash attack" but found the messages are the same set of errors that display if the device isn't properly plugged in.

"We're not saying the report is false. We're saying it's inconclusive because the evidence does not support their conclusions. We were able to generate the reported conditions without there being a security issue," said Kevin Fu, an associate professor of computer science and engineering and director of the Archimedes Center for Medical Device Security.

Fu is also cofounder of medical device security startup Virta Labs, which put together a separate, updated report, "Making Sense of Muddy Waters & MedSec." The report counters the short-seller's claims point-by-point and seems to argue the potential risks may be overblown.

On allegations related to the crash attack, the Virta Labs researchers provide explanations for the apparent loss of wireless connectivity, including potentially a disconnection between the radio subsystems from the therapeutic subsystems, which would meet FDA safety requirements. They also argue the crash may have triggered an automatic shutoff system to prevent excessive radio use.

In terms of the battery drain attack, Virta Labs says remediation actions such as an automatic radio shutoff system could be used to mitigate such risks. They also address other concerns raised by MedSec and Muddy Waters such as easily available firmware and software, credentials that could give malicious hackers access to St. Jude's Medical Networks, and the ability to use off-the-shelf hardware to crack the devices. On all counts, the researchers indicate these are common practices and the risks are overblown.

Larry Biegelsen, a senior analyst with Wells Fargo Securities, said they are encouraged by the report and are holding their forecast steady for St. Jude. Biegelsen also expects the much anticipated deal acquisition of St. Jude by **Abbott Laboratories Inc.** to go through later this year despite Muddy Water's allegations.

"The white paper does a nice job in our view of explaining why the allegations by Muddy Waters are not conclusive, in our view," said Biegelsen. "In addition, the authors of the white paper indicate that they find it plausible that [St. Jude] would be able to remediate most of the problems alleged in the Muddy Waters report through routine firmware updates."

ST. JUDE'S RESPONSE 'WEAK AND SHRILL'

However, not everyone is as optimistic as Biegelsen and Virta Labs. In a blog post for his company, wireless medical device expert Tim Gee, principal at Medical Connectivity Consulting, says the Muddy Waters report is "very credible" and implies the vulnerabilities to St. Jude devices may be more prevalent in the industry.

He argues the device-maker's responses are not specific enough and only deflect the bigger issues by nit-picking minor mistakes in the Muddy Waters report.

"These defensive assertions refute mistakes made in [Muddy Waters'] report, such as the transmission distance of pacemakers (50' in the lab, but much shorter when implanted due to the signal attenuation caused by water in the human body), and the behavior differences between unconnected pacemakers versus pacemakers connected to simulated leads and a patient's heart," said Gee. "The [St. Jude] response seems weak and shrill."

Gee also takes on the biggest criticism of Muddy Waters that it is behaving unethically to undermine St. Jude stocks so it can make a profit from the short-sale.

"Regardless what one thinks about the moral ethics involved in this practice, it is legal," he said. "The market provides incentives to firms like [Muddy Waters] to find and disclose bad actors that may have avoided disclosure as a consequence of corruption, graft or a successful avoidance of law enforcement."

ST. JUDE FILES SUIT

While FDA and others conduct assessments, the fight between St. Jude and Muddy Waters has escalated with the Minnesota-based device-maker suing the investor for intentionally disseminating "false and misleading information in order to lower the value of St. Jude Medical's stock and to wrongfully profit from a drop in share value through a short-selling scheme."

Muddy Waters stated the cyber-vulnerabilities would likely cause St. Jude to recall its devices or lead FDA to issue a forced recall. However, St. Jude has vigorously disputed their findings as fear-mongering for financial gain.

"We felt this lawsuit was the best course of action to make sure those looking to profit by trying to frighten patients and caregivers, and by circumventing appropriate and established channels for raising cybersecurity concerns, do not use this avenue to do so again," said St. Jude Medical CEO Michael Rousseau in a statement. "We believe this lawsuit is critical to the entire medical device ecosystem." ▶

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Abbott, Alere Agree To Mediation For Troubled Merger

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Abbott Laboratories Inc. and Alere Inc. are going to take their troubled merger effort before a mediator.

The companies announced plans for Abbott to pay \$5.8b for Alere, which would create the world's largest diagnostics company, on Jan. 30. But the deal has run into a series of challenges since then.

Last month, Alere filed suit against Abbott in Delaware Chancery Court to compel Abbott to complete the merger. Alere said that Abbott "breached the merger agreement between the parties by failing to promptly secure antitrust approvals and other regulatory requirements." Abbott denied the allegations.

Multiple federal investigations against Alere have delayed the company's required financial filings. Alere is facing scrutiny from the US Department of Justice into its Medicare billing and overseas marketing. In addition, the US Securities & Exchange Commission is looking at the company's accounting practices.

In the interim, Abbott announced plans to purchase **St. Jude Medical Inc.** for \$25bn in April.

Alere and Abbott announced that they would move to mediation in a Sept. 8 court filing, Reuters reported. Spokespeople for both companies confirmed the plan without further comment.

The current merger agreement gives Abbott up to eight more months to close the deal before the offer expires. The companies hope to move into mediation as soon as is possible. ▶

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VC DEALS ANALYSIS:

How Four Bad Months Can Spoil The Barrel

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Venture financing activity in 2016 is turning out to be a game of two halves. While the first four months saw their total deal value consistently beat the figures for 2015, things have taken a nose dive in the last four months, with August only raking in just over \$250m in total.

This is a far cry from the \$615m recorded in August 2015, although that month last year was admittedly a tough comparator, with two mega-buck deals of \$100m and \$200m. However, it is worth noting that August is typically a slow month, with this period usually recording the year's lowest takings (See Figure 1). Additionally, the total amount raised in August 2016 was still higher than that for the same month in 2014 and 2013.

August's weak performance could be attributed to the modest deal volume (22 deals of over \$1m), the second lowest this year so far after May, which recorded only 20 deals. But the deal size, as we all know, is what matters most, and August did not pull out any trump cards. (See Figure 2).

There were no deals over \$50m, nor any in the \$30-40m range. Instead, the majority of deals were concentrated on the lower deal size range and the biggest transaction was a \$46.5m growth-stage financing raised by **CVRx Inc.**, Minnesota-based CVRx's lead product is the CE-marked *Barostim NEO*, designed to electrically activate the baroreflex that regulates cardiovascular function. The device is indicated for patients with heart failure and high blood pressure – the company counts **Johnson & Johnson** among its investors (See Table 1).

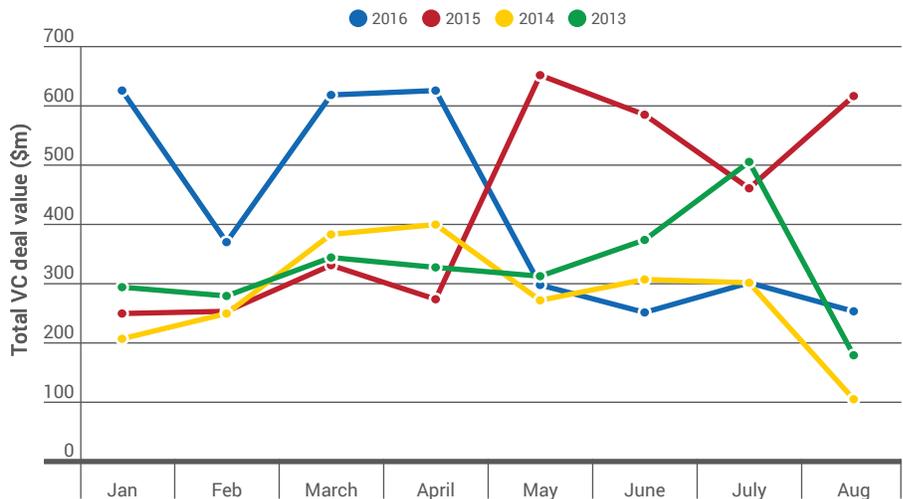
After CVRx, the second biggest deal is way behind at \$28m, raised by Massachusetts-based digital health company **Zillion**, which is developing an online platform to improve patient engagement and thus improve health-care outcomes.



CLICK
For more details about VC deals in 2016 and previous years <http://bit.ly/29DUQZu>

FIGURE 1

Total amount raised by month, Jan-Aug 2013-2016



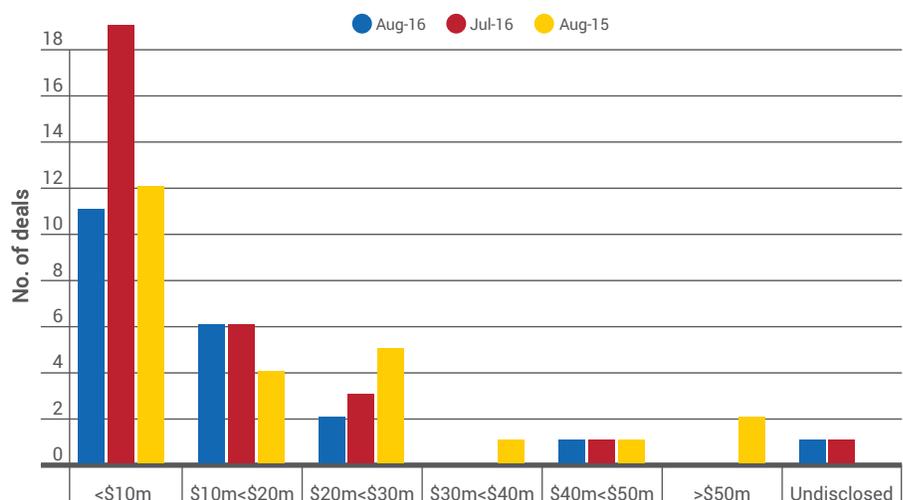
Source: Medtech Insight

	AUG. 2016	AUG. 2015	AUG. 2014	AUG. 2013
Total VC deal value* (\$m)	253.3	615.9	103.7	179.1

* Including only deals that disclosed financial details

FIGURE 2

No. of deals by amount raised



Source: Medtech Insight

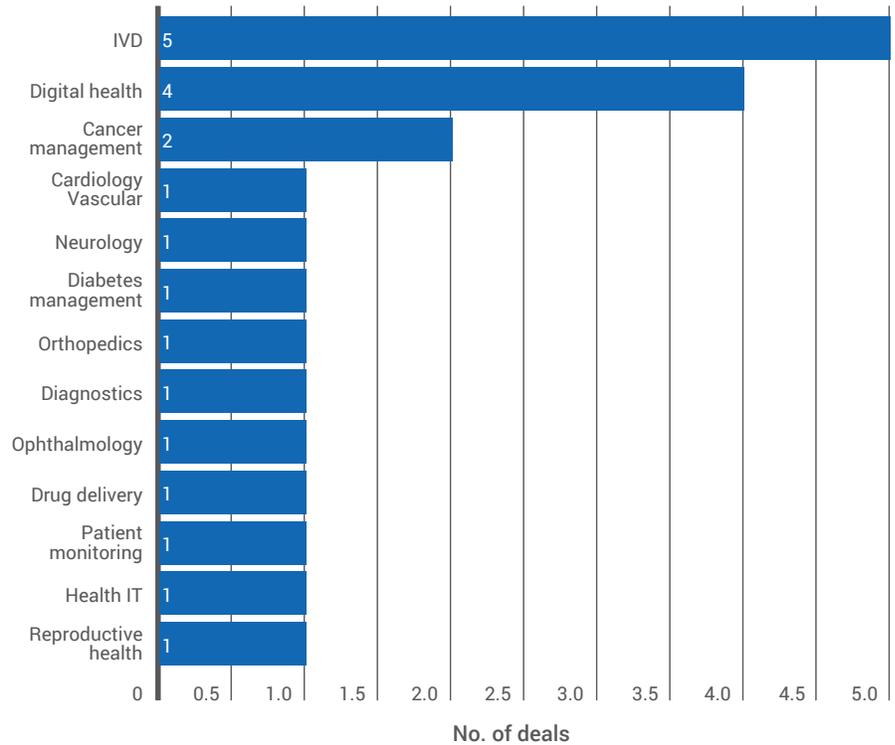
IVD, the most popular product/therapy sector for August with the most number of VC financing deals (see Figure 3), did not attract the biggest bucks. Two IVD companies just scraped into the month's top 5 rankings – **Singlera Genomics Inc.** raised a significant \$20m for its Series A, bucking the trend for typically small early stage rounds. It beat **Metabolon Inc.**, which raised \$15m in a Series E round.

As with July, the majority of deals were spread across a wide range of product/therapy sectors. Cardiology/vascular companies, which are usually among the more popular investments, came in fourth with only two deals, while digital health companies came in second, followed by firms developing cancer management solutions.

If VC investment activity for the rest of this year follows the pattern seen in 2013 and 2014, things should hopefully pick up over the next few months and there might be a chance that 2016 could still beat 2015. However, it would take a few nine-figure dollar transactions for this year to regain its lead; otherwise the outlook might not be too rosy.

FIGURE 3

Number of deals by product/therapy sector



From the editors of Clinica

Source: Medtech Insight

Top VC deals in in August 2016, by amount raised

RANKING	COMPANY	BASED IN	PRODUCT/THERAPY SECTOR	AMOUNT RAISED	FINANCING ROUND	TOTAL INVESTMENT
1	CVRx	MN, US	Neuromodulation/Cardiology	\$46.5m	Series G	Undisclosed
2	Zillion	MA, US	Digital health	\$28m	Series C	Undisclosed
3	Evofem	CA, US	Reproductive health	\$25m	Series D	Undisclosed
=4	Ornim	Kfar Saba, Israel	Patient monitoring	\$20m	Series C	Undisclosed
=4	Avelas Biosciences	CA, US	Cancer management	\$20m	Series C	Undisclosed
=4	Singlera Genomics	CA, US	IVD	\$20m	Series A	Undisclosed
5	Metabolon	NC, US	IVD	\$15m	Series E	\$80m

Source: Medtech Insight

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Pulmonx Reaches Multiple Milestones In Lung-Valve, Diagnostics Development

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The IMPACT trial shows **Pulmonx Corp.**'s *Zephyr* endobronchial valves produces clinically meaningful benefits in improved lung function, exercise tolerance and quality-of-life for patients with homogenous emphysema without collateral ventilation who were selected for the therapy with Pulmonx' *Chartis* diagnostic tool.

Results of the 93-patient IMPACT trial, led by Arschang Valipour of the Ludwig Boltzmann-Institute in Vienna, are published online in the *American Journal of Respiratory and Critical Care Medicine*. Co-principal investigator Rall Eberhardt of the Thoraxklinik at the University of Heidelberg in Germany presented the results at the European Respiratory Society meeting in London on Sept. 4.

The study randomized the patients with severe homogeneous emphysema and little or no collateral ventilation to either treatment with *Zephyr*, guided by *Chartis*, or to medical management. Three months after the treatment, the FEV1 scores – the volume exhaled during the first second of a forced expiration – were 17% better than the scores of patients in the control group. Patients in the *Zephyr* group also showed improved exercise tolerance as measured by a six-minute walk test and scored ten points better than the control group on the St. Georges Respiratory Questionnaire (SGRQ), a quality-of-life measure. Also, 97% of patients treated with *Zephyr* showed reduction in the volume of the lobe of the lung targeted in the treatment, demonstrating the immediate procedural success of the *Zephyr* implants.

This is the first randomized controlled trial to confirm that *Zephyr* is effective in patients with homogeneously distributed emphysema, as opposed to heterogeneous disease concentrated in a few areas. The IMPACT results "potentially doubled our addressable market," Beran Rose, Pulmonx' VP for marketing and business development, told *Medtech Insight*. "The received wisdom in the past is that only patients with a certain pattern of destruction by emphysema would be eligible for valves, because that was the criteria for patients eligible for a surgical procedure – which is infrequently used."

Rose says "It was taken as dogma that the valves wouldn't work in patients [with] a more uniformly distributed emphysema and would only work if you had one part of the lung where most of the destruction was, and you could just treat that part and leave all of the other parts alone." However, the IMPACT results show that patients with more evenly distributed emphysema derive similar benefits from *Zephyr* as the patients with concentrated damage. "It gives those patients a whole new treatment option [and] this brings hope to a whole bunch of patients who had very few options before."

Rose explained that after emphysema destroys part of the lungs, gas is trapped in those areas, taking up space and preventing new air from coming in. "So you have these patients with these really giant barrel chests, sometimes, but they're walking around completely breathless," Rose explained. "Often when they're di-

agnosed with stage 3 or 4 [severe or very severe] emphysema, their quality of life and prognosis is worse than that of the average lung-cancer patient. It's really a terrible quality-of-life."

The *Zephyr* EBV is a small implant, which Rose described as "a stent covered in silicone and with a duck-billed valve." It is designed to be placed in the lungs with a minimally invasive procedure to block airflow to diseased regions, which allows these patients to reduce their overall lung volume and breathe easier. *Zephyr* is CE-marked, but not yet available in the US.

IMAGING-GUIDED PROCEDURE

In the *Zephyr*-implant procedure, the treating physician deploys the *Chartis* imaging system via bronchoscope to determine if the patient has low or no collateral ventilation from an area of their lungs, indicating that the patient may respond well to the treatment. If the *Chartis* finds a place where *Zephyr* can be effective, the physician can deliver the valve using the same pathway. *Chartis* has a CE mark and earned a 510(k) from US FDA in 2009.

Once *Zephyr* is deployed, air will leave that lobe of the lung, but won't return. This will give the patients' lungs more room to expand and contract and let the patient breathe better overall. "We've seen now across four randomized trials [that] patients feel dramatically better and able to do more exercise [following this treatment]."

Rose said Pulmonx hypothesized *Zephyr* could treat patients with homogenous emphysema in addition to those with heterogeneous emphysema after retrospectively analyzing results from VENT, a trial of endobronchial valves originally sponsored by *Zephyr*'s developer, **Emphasys Medical Inc.**, which Pulmonx acquired in 2009.

VENT was designed to enroll only patients with heterogeneous emphysema, but advanced imaging analysis showed that many of the patients in the trial actually had homogenous disease, Rose explained. Then, results of the STELVIO trial, the first randomized controlled study of *Zephyr* in severe emphysema patients selected using the *Chartis* system, also indicated that patients with homogenous disease benefit from *Zephyr*. The primary STELVIO results, announced at the American Thoracic Society meeting in May, showed that 65% of patients treated with *Zephyr* experience clinically meaningful improvement in lung function at one year.

Following the advice of its advisory panel, FDA denied *Emphasys Medical*'s application for approval of *Zephyr* in 2009, citing questions about the long-term data submitted by the company. To support a new FDA application for *Zephyr*, Pulmonx is sponsoring LIBERATE, a randomized trial comparing *Zephyr* to optimal medical management in about 180 patients with heterogeneous severe emphysema. The enrollment will be complete in September and the primary follow-up will be complete in a year.

TOWARD A COMPLETE PERSONALIZED APPROACH TO EMPHYSEMA

“The larger goal of our company is to enable personalized treatment for each of these emphysema patients. When the physician can get information about that specific patient’s lung, then they can decide on the best treatment for this particular patient based on that information with clinical data on those different treatments across those different phenotypes of patients,” Rose explained. “I think that makes us somewhat unusual in the device intervention space, but it’s definitely part of a larger trend that you see, and not just in respiratory medicine, but across the board: tailored personalized care.”

On Sept. 1, the company announced the commercial launch of its *StratX* lung-analysis platform in countries requiring the CE mark. *StratX* is a cloud-based service that provides accurate analysis of computed tomography scans of the lungs to determine if the patient is suitable for endobronchial valve treatment. *StratX* can reliably and efficiently identify patients with complete fissures – the divisions between the lobes of the lungs who will likely benefit

from endobronchial valve treatment, and distinguish them from patients whose fissures are below 80% complete, and therefore not amenable to that therapy. Patients whose fissures are 80% to 95% complete are subject to further diagnostic analysis.

Prior to this type of analysis, physicians tended to simply “eyeball” their patients’ lung CT scans to determine if they were suitable for endobronchial valve therapy, leaving some potential good candidates without effective treatment, Pulmonx explains. “We see that potentially improving care and expanding our market,” Rose said. “That brings us closer to this vision of personalized care, [and] we anticipate continuing to add new functionality to it in the future as we add more therapeutic tools to the tool bag and learn more about the best way to target interventions to specific areas of the lung.”

Pulmonx is also developing the *AeriSeal* lung sealant system for treating emphysema, which it acquired as part of its February 2015 buyout of **Aeris Therapeutics Inc.** ▶

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◀ COVER STORY ▶

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end of the decade. However, the largest potential market for liquid biopsy would be its use as a screening tool, for testing the general asymptomatic population for particular types of cancer. Although this application is not likely to take off before 2020, it could eventually be worth as much as \$9bn annually, they say.

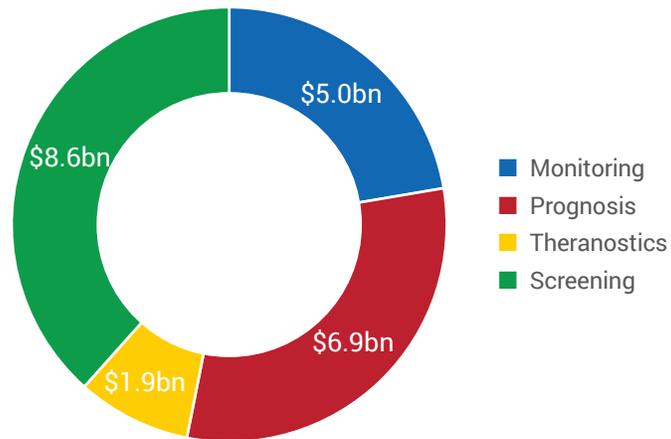
DRIVERS AND CHALLENGES

While there are a number of factors driving the uptake of liquid biopsy, the JP Morgan analysts also identify a several challenges. Among the drivers is the improved patient experience from a noninvasive approach to molecular profiling of a tumor compared with tissue biopsy, especially for patients who require serial biopsies, for example to monitor the development of drug-resistant mutations. In addition, the liquid biopsy approach is potentially less expensive than a tissue biopsy, as it does not require the same level of highly trained professional to obtain the sample, and offers a quicker turnaround time.

On the other hand, the key challenge to uptake of liquid biopsy is the cost of actual sequencing: at present, it is only possible to obtain an adequate depth of sequencing at a cost that is too expensive for routine clinical use. However, just as the cost of whole genome sequencing has fallen

FIGURE 1

Total liquid biopsy market, 2020



Source: JP Morgan

dramatically, so will the cost of sequencing DNA from liquid biopsy samples.

An additional hurdle that needs to be overcome is a lack of physician and insurer awareness of liquid biopsy. It is still a relatively new technology, and health professionals are only just beginning to appreciate the benefits that liquid biopsy may bring. Similarly, until the technology is more widely accepted, there are likely to be reimbursement issues associated with its use.

A number of companies are already marketing liquid biopsy products for use in

cancer management, and several others have revealed plans to enter the market. However, those that have already put a toe in the water tend to be in the early stages of product ramp-up or have had limited experience in commercializing such products so far, the JP Morgan analysts state.

Companies in this sector break down into several broad categories. There are those with systems that cap-



CLICK
to see the potential benefits of CTCs
<http://bit.ly/2c7eLvp>

ture circulating tumor cells (CTCs) in the bloodstream for use as a biomarker in liquid biopsy; those that offer sequencing platforms *per se* for analyzing the CTCs or circulating tumor DNA (ctDNA) biomarkers; those that offer next-generation sequencing (NGS) instrumentation; and those that operate reference laboratories offering liquid-biopsy testing.

CTCS AND CTDNA

Of the different types of marker used in liquid biopsy assessment of cancer patients, the oldest and most highly developed technique is the analysis of CTCs – cancer cells that detach from a primary tumor and travel through the bloodstream or lymphatic system to other parts of the body. Their presence, which can often be detected quite early in the course of the disease, is a fundamental prerequisite to metastasis, and their enumeration thus offers great potential for diagnosing cancer patients but also in assessing prognosis. Furthermore, the molecular characterization of CTCs can provide considerable information about things like the sensitivity of the primary tumor to treatment and its potential for developing resistance to anticancer agents.

Until recently, however, the potential of CTCs as an aid to cancer management was limited by the low abundance of the cells; detecting and counting them has been compared with finding a needle in a haystack. That has not stopped companies from trying to develop CTC capture systems that can harvest enough of the target cells as well as maintain the integrity of the cells. **Janssen Diagnostics LLC's CellSearch** CTC test was originally cleared by US FDA for *in vitro* diagnostic use in 2004 and, 12 years later, several firms are at different stages of taking their CTC system to market. (See Table 1).



CLICK HERE
to see Table 1 and the list of CTC capture companies <http://bit.ly/2c7eLvp>

One such company is UK-based **ANGLE plc**. Its lead product is the *Parsortix* cell separation system, which uses a patented microfluidic system in the form of a disposable microscope slide-sized cassette

to capture and then harvest CTCs from blood. The separation process is predicated on the larger size and less deformable nature of CTCs compared with other blood components.

In the Parsortix system, CTCs are trapped on a step that crisscrosses the cassette, where they can be fixed and stained to allow identification and enumeration. And because Parsortix uses a label-free approach that does not require an antibody to bind to the CTC, the captured cells can be used for downstream genetic analyses such as quantitative PCR sequencing.

Parsortix is CE-marked for use as an *in vitro* diagnostic device in the EU, but the company, so far, is commercializing it for research use only and is conducting several programs to build evidence of Parsortix's utility as a clinical diagnostic tool. Angle has partnered with several research and medical institutions to investigate the use of its system as a diagnostic tool for several cancers, ovarian cancer being its most advanced program, followed by breast and prostate cancer. The company is also working towards gaining US clearance for Parsortix.

Many liquid biopsy approaches target circulating tumor DNA, rather than whole CTCs, as the biomarker. ctDNA is cell-free DNA that is shed from tumor cells into the circulatory system. Cell-free DNA occurs in a number of other conditions, including renal failure and myocardial infarction, but ctDNA is distinguished by the presence of specific somatic mutations that appear to correlate with mutations in tumor DNA. The mechanism by which ctDNA enters the circulation is not fully understood: it may be secreted by viable tumor cells, it may arise as a consequence of tumor cell death under the effect of chemotherapy, or it may be released by phagocytes that have engulfed tumor cells. Whatever its origin, it only has a half-life in blood of perhaps one or two hours: it is typically between 180 and 200 base pairs in length.

Like CTCs, ctDNA has several advantages over tissue biopsy as a source of cancer biomarkers, including quick and easy collection, low risk of complications such as pain or infection, and a better reflection of tissue heterogeneity in tumors

– gene expression often varies in different parts of the same tumor, so while taking a biopsy from a single site may give an incomplete picture, circulating ctDNA gives a snapshot of the tumor genome overall.

SEQUENCING PLATFORMS

Another company in the liquid biopsy space is **Biocept Inc.**, which develops cell-free tests using proprietary technology to capture and analyze ctDNA in both CTC and plasma. It offers NGS-based tests for assessing targeted mutations in non-small cell lung cancer (NSCLC) and gastric and breast cancers as well as a test based on NGS to monitor breast cancer patients. It also offers tests for colon and prostate cancer and melanoma.

In May 2016, Biocept launched its *Liquid Biopsy Immuno-Oncology PD-L1 Test*, which uses the company's *Target Selector* platform with CTCs from a patient's blood sample to detect and monitor PD-L1 protein expression throughout the course of a patient's cancer therapy. Patients with cancers that express the PD-L1 protein are more likely to respond to immunoncology therapeutics such as **Merck & Co. Inc.'s Keytruda** (pembrolizumab), which was recently approved for use in patients with advanced NSCLC who test positive for PD-L1 expression using **Dako North America's PD-L1 IHC 22C3 pharmDx** immunohistochemical assay, based on testing of formalin-fixed, paraffin-embedded NSCLC tissue.

Launch of its PD-L1 test came just days after Biocept introduced a test to detect *RET* oncogene fusions in blood samples from patients with lung cancer. Positive identification of patients with the *RET* gene can help guide treatment with tyrosine kinase inhibitors.

Michael Nall, Biocept's president and CEO, commented that the new Liquid Biopsy PD-L1 test is one of the few, if not the only, commercial, CLIA-validated, blood-based test for detecting PD-L1 expression. He said that the test provides a new option for physicians to qualify patients for approved immuno-oncology therapies and for companies developing such products (Ono, Novartis and Pfizer are among the companies developing anticancer agents that act in a similar way to Keytruda).

Biocept works closely with pharma companies. In March of this year it announced a collaboration with an unspecified biopharmaceutical company on a clinical trial analyzing biomarkers using both CTCs and ctDNA from cerebrospinal fluid. The trial is being conducted in patients with NSCLC whose disease has spread to the brain or meninges, a condition known as leptomeningeal disease. In May, Biocept said it had entered a multi-project Master Services Agreement whereby it is developing research and clinical trial assays for a large pharma organization.

Biocept plans to introduce further CLIA-validated tests in the near term. Nall told *Medtech Insight* that the company has already commercially launched 10 other assays that have undergone rigorous analytical and clinical validation in its CLIA laboratory. "The goal is to offer medical oncologists and the patients they care for the same NCCN [National Comprehensive Cancer Network] guideline-based biomarkers used for clinical decision making via liquid biopsy that are traditionally performed on a tissue biopsy. In addition, we offer many other markers for both Pharma and academic research."

Another early mover in the liquid biopsy area is **Trovagene Inc.** which, like Biocept, is headquartered in San Diego, California. Trovagene is one of the few market participants focused on developing urine-based liquid biopsy tests, although it does also produce blood-based tests. The company points to the advantages of urine over blood: samples can be collected conveniently in the patient's own home, there is a virtually unlimited sample supply, and information about treatment can be obtained faster and more often. Indeed, Trovagene has registered the trade mark "Yellow is the new red".

Trovagene's platform technology is a polymerase chain reaction-based technique known as *Precision Cancer Monitoring* (PCM), and is the basis of its CLIA and CAP-accredited Trovera line of urine- and blood-based liquid biopsy tests for quantifying oncogenic mutations of genes such as *EGFR* (for lung cancer), *KRAS* (for lung, ovarian, pancreatic and colorectal cancers) and *BRAF* (for melanoma, Erdheim-Chester

disease and Langerhans cell histiocytosis, two rare conditions related to leukemia).

Trovagene's technology includes a novel enrichment technique optimized for small DNA fragments in urine, and has been validated in a number of studies published over the past two years or so. "We have demonstrated the analytic performance of our test as well as the clinical performance," Mark Erlander, Trovagene's chief scientific officer told *Medtech Insight*. Most recently, at the 2016 American Society of Clinical Oncology (ASCO) meeting in Chicago, Illinois, clinical results demonstrating highly sensitive detection of *EGFR* T790M mutations in the urine of patients with NSCLC were presented. "Trovagene's urinary ctDNA test was able to identify the *EGFR* resistance mutation in cases not detected in tissue," said Karen Reckamp, one of the lead investigators. "The data suggest that urinary and plasma *EGFR* analyses complement tissue biopsies in *EGFR* tyrosine kinase inhibitor (TKI) resistant NSCLC."

Although *EGFR*-TKIs such as erlotinib (**Astellas Pharma Inc.**'s *Tarceva*), afatinib (**Boehringer Ingelheim GMBH**'s *Gilotrif*) and gefitinib (**AstraZeneca PLC**'s *Iressa*) have demonstrated response rates as high as 80% in patients with NSCLC, most tumors subsequently develop resistance related to the T790M mutation. Last November the FDA approved osimertinib (AstraZeneca's *Tagrisso*) for the treatment of NSCLC patients with this mutation: several other drug candidates are in development for this indication.

Like Biocept, Trovagene has worked with a number of pharma companies in this area, including a partnership with Clovis Oncology as part of the diagnostic arm of a third generation tyrosine kinase inhibitor development program. In addition, the company is engaged in numerous clinical collaborations with leading cancer centers and academic institutions. Its technology is backed by a "robust" intellectual property portfolio, Dr Erlander said.

Rather than look for specific changes in genes or protein expression, San Jose, California-based **Chronix Biomedical Inc.** has developed technology that takes a more holistic approach by measuring chromosomal gains or losses in cell-free

DNA and calculating the genomic copy number instability index (CNI). The CNI technique is based on sequencing studies conducted by the company showing that, among 500 cancer patients and a similar number of matched controls, the main difference was not, as expected, at the level of individual single nucleotide polymorphisms but in regions on the genome where the number of DNA fragments differed between the two groups. In other words, if there are more or fewer DNA fragments in one area of the test genome compared to the same area of a matched control genome, this represents genomic instability caused by bad local DNA repair, which is indicative of cancer.

The company's *Delta Dots* test is designed to calculate the CNI score as an indicator of how well the patient is responding to cancer therapy. Earlier in April, at the American Association for Cancer Research meeting in New Orleans, Louisiana, data from a 24-patient, blinded proof-of-concept study showed that *Delta Dots* was able to correctly stratify patients as either responders or non-responders to chemotherapy in 92% of cases, compared with the industry standard for measuring cancer treatment response (RECIST). Chronix is also investigating *Delta Dots* for measuring response in two other types of cancer therapy: immunotherapy – the company had presented early data for this indication at ASCO in June – and radiotherapy. Evidence from Chronix's studies of *Delta Dots* have suggested that the test can predict the patient's response to therapy as early as two weeks, which mean physicians can change the patient's treatment earlier if required to a regime that is more effective.

As well as the *Delta Dots* test, Chronix offers the *Second Opinion* supplemental test for breast and prostate cancer. However, rather than replace mammography or PSA testing, *Second Opinion* is intended to provide additional information that can be used with the CNI score to assist doctors' decision-making.

The company is also seeking to develop a "pan-cancer test", which would be able to screen asymptomatic patients for cancer. This is based on the principle that "if

you have gains or losses in your blood, you have cancer somewhere," Chronix CEO Howard Urnovitz had told *Medtech Insight* in an interview earlier this year.

MORE ESTABLISHED PLAYERS

The liquid biopsy area has also attracted more established diagnostics companies such as Hilden, Germany-based **Qiagen NV**, a global leader in technologies for the extraction and isolation of nucleic acids from biological samples. In 2015, Qiagen introduced the world's first regulated companion diagnostic for lung cancer based on liquid biopsy, the CE-marked *therascreen EGFR* RGQ Plasma PCR kit, which was developed in collaboration with AstraZeneca and paired with AZ's Iressa. The test enables *EGFR* mutation profiling in patients for whom surgical biopsy is not an option, thereby permitting physicians to select patients who could benefit from Iressa treatment. Also in 2015, Qiagen launched a fully automated protocol for isolation of ctDNA from human plasma on the *QIAasymphony* platform for research applications.

In March 2015 Qiagen acquired technology from the German company **AdnaGen AG** that enables enrichment and molecular analysis of CTCs from blood samples. At the same time, Qiagen entered a partnership with **Tokai Pharmaceuticals Inc.** to co-develop a companion diagnostic using the CTC technology to guide the use of Tokai's androgen receptor modulator/lyase inhibitor galeterone, which is in Phase III trials for treatment of castration-resistant prostate cancer.

In addition, Qiagen is collaborating with **Exosome Diagnostics Inc.** to develop products for the extraction of exosomes from blood and other body fluids. A kit for the isolation of RNA from plasma or serum to analyze mutations and gene expression profiles was introduced in 2014 for use in cancer research. The companies are also working on a non-invasive test for the analysis of key biomarkers in NSCLC and other malignancies: this test could potentially be developed into a companion diagnostic for several new cancer drugs.

Michael Kazinski, senior director and head of Qiagen's liquid biopsy franchise for life sciences, told *MedTech Insight* he sees point-of-care testing as a likely application for the future of liquid biopsy technology. "Acceptance will rely on easy-to-perform assays and on standardization of sample collection and stabilization procedures," he said. "Further, automation will be of increasing importance for cost and standardization reasons." Kazinski also expects a clearer picture to emerge on which analytical domain (CTC vs ctDNA) is the most appropriate to use for the various applications, and a stronger utilization of NGS-based assays.

Sysmex Inostics GMBH, the molecular diagnostics subsidiary of Sysmex Corp, is another established diagnostics outfit that has been drawn to liquid biopsies. It is collaborating with **Merck Serono SA** on the introduction of the *OncoBEAM RAS* digital polymerase chain reaction assay, which detects ctDNA in blood or plasma and which is designed to provide information on the patient's *RAS* mutation

TABLE 2

Companies selling or developing liquid biopsy tests for oncology

COMPANY	TECHNOLOGY	APPLICATION(S)
Abbott	UroVysion Bladder Cancer kit detects aneuploidy for chromosomes 3, 7 and 17 and loss of the 9p21 locus via fluorescence in situ hybridization in urine sample	Bladder cancer
Aspira Labs (a Vermillion company)	OVA1 test measures five ovarian cancer biomarkers	Screen for ovarian cancer in patients with adnexal mass
Beckman Coulter	phi (prostate health index) based on three PSA markers	Prostate cancer
Biocept	Isolation and analysis of CTCs/ctDNA using real-time PCR	Currently gastric, breast, lung and other cancers
Caris Life Sciences	Carisome TOP platform	Isolation of circulating microvesicles
Chronix Biomedical	Copy number instability index	Identifying responders/non-responders
Cynvenio	ClearID genetically analyzes both CTC and ctDNA	Breast cancer
Exosome Diagnostics	Sequencing of exosomal RNA or DNA	Prostate cancer, lung cancer and solid tumors
Foundation Medicine	NGS-based oncology panels	Solid tumors; hematologic malignancies
Genomic Health	ctDNA in urine	Bladder cancer
Guardant Health	NGS-based tests using Digital Sequencing filtering method	Lung, breast, colorectal and other cancers
Hologic	Progenesa prostate cancer gene 3 (PCA3)/PSA RNA assay	Prostate cancer

COMPANY	TECHNOLOGY	APPLICATION(S)
Inivata	InVision amplifies panel of 34 selected cancer-related genes	Various cancers
Matritech	NMP22 Bladderchek measures nuclear matrix protein in urine	Bladder cancer
MDxHealth	Real-time quantitative PCR	Urologic cancers
Myriad Genetics	BRCAAnalysisCDx	Companion diagnostic to help identify advanced ovarian cancer patients who may benefit from treatment with Lynparza (olaparib)
Onocyte	Analysis of proprietary cancer markers using proprietary algorithm	Lung and breast cancer
OPKO Health	Prostate-specific kallikrein assay in blood	Risk of aggressive prostate cancer
Pacific Edge	Cxbladder measures five specific mRNA biomarkers in urine	Bladder cancer
Personal Genome Diagnostics	MYPG	Comprehensive analysis of cancer genomes
Qiagen	therascreen EGFR RGQ Plasma PCR kit	Companion diagnostic test for AstraZeneca's Iressa
RainDance	RainDrop digital PCR instruments and consumables; sample prep for NGS	Minimal residual disease in AML patients
Resolution Bioscience	NGS-based tests to sequence mutations in most commonly found genes	Lung and other cancers
Roche (thru acquisition of CAPP Medical)	DNA sequencing	Cancer (unspecified)
Trovogene	Digital droplet polymerase chain reaction (ddPCR)	Companion diagnostics to detect mutations on tumor-related genes (<i>BRAF</i> , <i>KRAS</i> , <i>EGFR</i>) to assist in choice of cancer therapy and to detect 13 high-risk HPV types from urine
Veracyte	Percepta Bronchial Genomic Classifier	Lung cancer

status. Tissue-based testing for *RAS* mutations normally takes several weeks, but the Sysmex test is expected to provide results within days. Approximately 50% of patients with metastatic colorectal cancer have tumors with *RAS* mutations, and anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody therapies, such as Merck's Erbitux (cetuximab), may improve outcomes in metastatic colorectal cancer with the wild-type *RAS*. The test is already available in Italy.

The potential of liquid biopsy in the management of cancer has also been recognized by **Illumina Inc.**, a major player in the DNA sequencing and array-based technology sectors. At the beginning of this year it formed a majority-owned new company, **Grail**, whose stated mission is

to enable cancer screening from a simple blood test. The aim is to use Illumina sequencing technology to develop a pan-cancer screening test by directly measuring ctDNA in blood.

Grail was initially funded by more than \$100m in Series A financing from Illumina and **ARCH Venture Partners**, with participating investments from Bezos Expeditions, Bill Gates and Sutter Hill Ventures. The company says its unique relationship with Illumina provides the ability to sequence economically and at the depths necessary to create a screening test with the needed sensitivity and a hoped-for level of specificity hitherto unavailable for cancer screening.

Table 2 summarizes the established and emerging companies in liquid biopsy for oncology.

REFERENCE LABS

Big testing labs too have been attracted to liquid biopsy. For example, **Laboratory Corp. of America Holdings** (LabCorp), one of the largest independent clinical laboratory companies in the US, offers not only a menu of several hundred routine tests to physicians, hospitals, governmental agencies and pharmaceutical companies, but also esoteric testing in a number of areas such as cardiovascular disease, infectious disease and oncology. In the latter area the company offers advanced comprehensive tumor tissue analysis through its Dianon Pathology and Integrated Oncology specialty testing laboratories. It also provides access to the latest pharmacogenetic tests: in June 2016 LabCorp announced the availability of the

Roche cobas EGFR Mutation Test v2, the first blood-based test approved for clinical use in the US to detect certain *EGFR* gene mutations in NSCLC patients (it was approved by the FDA on June 1, 2016).

Other reference labs are also jumping on the bandwagon. **NeoGenomics Inc.**, which operates a network of CLIA-certified clinical laboratories that specialize in cancer genetics testing, expanded its liquid biopsy offering at the end of last year with the launch of two new tests for monitoring solid tumors and predicting drug resistance, bringing the total number of liquid biopsy tests available to 15. The *NeoLAB Solid Tumor Monitor* is an NGS-based test that analyzes ctDNA to quantify and track genomic abnormalities in patients with documented metastatic cancer who carry specific abnormalities already confirmed by tissue biopsy testing. Results obtained with the test can be used to capture the heterogeneity in the cancer, monitor the emergence of new resistant clones, and predict relapse.

The *NeoLAB BTK Inhibitor Acquired Resistance* test is designed to predict resistance to Bruton's tyrosine kinase (BTK) inhibitors such as **AbbVie Inc.'s Imbruvica** (ibrutinib). Resistance to BTK inhibitors is associated with mutations in the *BTK* and *PLCG2* genes. The test can detect mutations in these two genes prior to tissue or cell-based testing, and can be used to monitor patients treated with BTK inhibitors, especially in chronic lymphocytic leukemia, mantle cell lymphoma and diffuse large B-cell lymphoma. NeoGenomics claims mutations in *BTK* and *PLCG2* can be detected up to 12 months before the appearance of overt clinical resistance to therapy.

Other liquid biopsy products available from NeoGenomics include a series of NGS-based assays for the detection and measurement of biomarkers in the peripheral blood plasma of patients with known or suspected hematologic cancers, and a blood- and urine-based test designed to be used as an adjunct to PSA testing to diagnose the presence of prostate cancer and to distinguish high-grade from low-grade cancer to help inform whether a biopsy is needed. "The overall market for oncology testing is growing and is contributing to our company

growth," says NeoGenomics' chairman and CEO, Douglas M VanOort. The company increased testing volumes in its base business by 25% last year, and is looking to better that performance this year following the acquisition of Clariant from GE in December 2015.

BEYOND CANCER - NIPT

Another company offering cancer diagnostics based on liquid biopsies is San Carlos, California-based **Natera Inc.** What sets Natera apart from many companies offering liquid biopsy oncology tests is that it is also involved in the non-invasive prenatal testing (NIPT) sector. Of particular note is its *Panorama* prenatal screening test, the only commercially available NIPT that utilizes single nucleotide polymorphisms (SNPs) to analyze chromosomal abnormalities. This allows the test to distinguish between fetal (placental) and maternal cell-free DNA, thereby delivering higher sensitivities than other tests, the company says.

The *Panorama* test is based on a blood sample from the mother and a comprehensive panel of chromosomal aneuploidies and other chromosomal variations. It provides what the company claims are the most accurate results of any screening test, as early as nine weeks into the pregnancy, which can help healthcare providers and patients decide whether more invasive testing, such as amniocentesis and chorionic villus sampling, is appropriate.

Other companies working on technology for NIPT include LabCorp, Illumina, and **Quest Diagnostics Inc.** (See Table 3.) This is an attractive segment to operate. With around five million pregnancies each year in the US – leading to approximately four million live births – and assuming peak penetration of about 70% of the potential market, and a unit cost of around \$400, the total market in the US could approach \$1.5bn.



According to analysts at financial services firm Cowen Group, the NIPT market breaks down into two segments: high-risk pregnancies and average-risk pregnancies. The

high-risk segment is already more than 50% penetrated, they say, and growth this year is therefore likely to be in single figures. On the other hand, penetration of the average-risk segment is still below 10%, and this therefore potentially offers better growth opportunities. However, the analysts say, growth will depend on NIPT being reimbursed for this population segment and becoming recognized in formal guidelines (such as those of the American College of Obstetricians and Gynecologists) for the management of average-risk pregnancies.

Qiagen's Kazinski comments that, although oncology is the most promising area of application for liquid biopsy technology, NIPT is currently the most advanced. "In the future we also see application potential in transplant rejection and other nonmalignant diseases, he said.

Lastly, it is worth mentioning that liquid biopsy technologies may turn out to have a role in the management of conditions such as kidney disease as well. While urinary proteome analysis potentially holds much information about the condition of the kidney, there is something of a question mark over how easily proteomic information can be obtained, and whether it could be accepted into routine use. Most of the research in this area centers on chronic kidney disease (CKD), the most prevalent form of kidney disease, and a large multicenter trial aimed at preventing CKD through urinary proteomics-directed intervention (the PRIORITY trial) has recently been launched. As such, efforts to develop liquid biopsy in nephrology are in their infancy.

For the moment, then, the focus is on oncology. "Over the next five years, liquid biopsy tests have the potential to evolve into the standard of care for physicians in patient cancer detection and monitoring," says Trovogene's Erlander. "The ability to detect ctDNA, whether in urine or blood, early enough may lead to earlier intervention and earlier treatment." Liquid biopsy is still an emerging technology, and one, moreover, that faces barriers to its wider acceptance, such as reimbursement issues, but the benefits it can offer seem likely to ensure that the sector is set for steady growth. ▶

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