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Ambulatory ECG Monitoring Enters a New, More Patient-Friendly Era

Digital Technologies Shake Up Arrhythmia Monitoring Part 2

by
MARY THOMPSON

The arrhythmia monitoring market is undergoing a digital health-driven transformation, and the implications for the wider medtech industry could be substantial. In Part 2 of this two-part article, we discuss the competitive landscape in arrhythmia monitoring, the unmet needs driving tech-enabled solutions, and what the future could hold for this space.

KEY POINTS

- A new generation of patient-friendly digital cardiac arrhythmia monitoring devices has the potential to expand the reach of what is already a multibillion-dollar market.
- Apple recently entered the field with an ECG-enabled watch, but will the tech giant's lack of a footprint in healthcare hamper its ability to compete against established players like Medtronic, Abbott, and iRhythm?
- Using digital monitoring technologies to screen for AF in high-risk asymptomatic patients could lead to better health outcomes, but it's not clear yet whether the benefits of such screening outweigh the potential risks.
- As high-tech and medtech continue to converge, the broader medical device arena could glean some important lessons from arrhythmia monitoring's digital health transformation, which is an important proving ground for future patient-centric care paradigms and more cost-effective, real-world clinical trials.

Much has been said about the potential impact of digital health, artificial intelligence (AI), and other high-tech advances on the patient care paradigm, and some clinical spaces—diabetes is perhaps the best example—have already widely embraced a more high-tech, connected, and patient-centered care model. (*See "Diabetes Devices: A Market in Transition,"* MedTech Strategist, *October 12, 2017.*) But diabetes is far from the only medical device market that is ripe for a digital health transformation. Another good example can be seen in cardiac arrhythmia monitoring, where a variety of ambulatory electrocardiogram (ECG) devices are employed to help diagnose patients with suspected heart rhythm disorders, including the most common clinically actionable arrhythmia, atrial fibrillation (AF).

Arrhythmia monitoring has long been a problematic area of healthcare and definitely not one known for an efficient or patient-friendly approach. Standard Holter monitors—the most commonly used ambulatory monitoring tools—are bulky, with multiple wired leads that must be attached to the chest and limited data collection capabilities. And traditional service-based monitoring solutions—such as those staffed 24/7 with technicians who monitor ECG data coming from cardiac telemetry devices—are costly and labor intensive. However, ongoing technology advances, including sensor miniaturization, wireless connectivity, and machine learning algorithms, have ush-

ered in a new era in ambulatory ECG monitoring, spawning a burgeoning field of more patient-friendly, digital wearable and implantable alternatives. And that is shaking up the status quo—transforming patient care, clinical trial paradigms, and longstanding market dynamics.

Ambulatory monitoring was developed to aid in the diagnosis of AF and other transient, difficult-to-detect arrhythmias. It is most often employed today in patients who have symptoms suggestive of an arrhythmia problem, such as palpitations, dizziness, shortness of breath, or unexplained fainting (syncope). However, there is an effort by some to push arrhythmia monitoring into asymptomatic patient populations, particularly those that may be at high-risk for AF. Although screening among asymptomatic groups remains controversial and the risks/rewards are not yet clearly defined, the aim is to identify individuals with undiagnosed AF who could benefit from treatment to reduce their risk of serious adverse events.

Among people with AF, the greatest risk is thromboembolic stroke—AF increases stroke risk up to five-fold and causes an estimated 15-20% of all ischemic strokes, according to the US Centers for Disease Control and Prevention. AF patients at high risk of stroke are commonly treated with anticoagulant drugs as a preventive measure, but even lower-risk AF patients can reduce their stroke risk with certain lifestyle changes (such as weight loss and treatment of sleep apnea). However, they can't be treated if they aren't diagnosed, and according to researchers, a substantial number of people—in both high- and low/intermediate risk categories—are walking around with subclinical (asymptomatic) undiagnosed AF. In fact, recent data from the ASSERT II trial suggests that the prevalence of undiagnosed AF could be as high as 30% in people age 65+ with other risk factors (see Morillo, CA et al. Atrial fibrillation: the current epidemic. *J Geriatr Cardiol*. 2017 Mar; 14(3): 195–203). Thus, there is an urgent need to better understand the role of ambulatory screening in these at-risk populations. (*For more on AF, see "AF Ablation After CABANA: What Are We Missing?"* MedTech Strategist, *August 24, 2018 and "New Atrial Fibrillation Mapping, Information Systems Lay Down Evidence Base,"* MedTech Strategist, *September 28, 2018*.)

Branching into these new indications could add substantial future growth prospects to an existing US ambulatory arrhythmia monitoring market currently valued at $1.4 billion annually and growing in the double-digits. There are several product segments in this space, all of which are seeing an influx of more patient-friendly digital technologies. Holter monitors, which record continuous ECG data, account for the largest segment of the market, with about 2.8 million tests performed per year in the US, followed by event monitoring, mobile cardiac telemetry (MCT), and implantable loop recorders (also known as insertable cardiac monitors, or ICMs), according to **iRhythm Technologies Inc.**, a fast-growing digital arrhythmia monitoring company that pioneered leadless, wearable (patch-based) long-term continuous monitoring (*see Figure 1*).

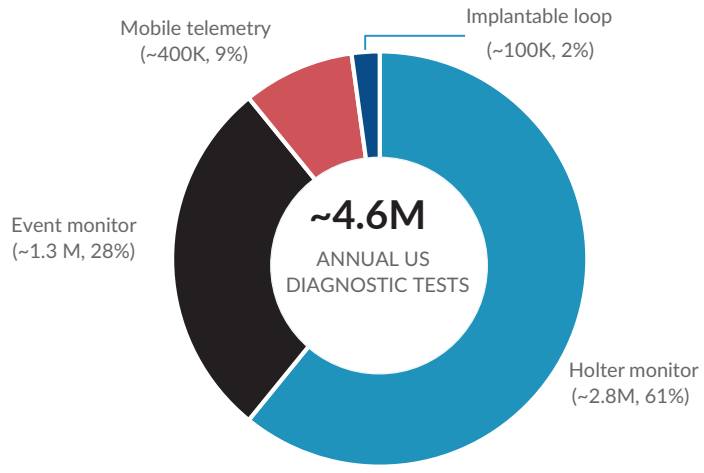
Expanding Options

Competitors in this space range from young companies like iRhythm to established medtech giants such as **Medtronic plc**, and the pipeline is full of new tech-enabled devices and solutions (*see Figure 2*). In addition, several big names in the tech field are targeting the space as well. **Apple Inc.** is the first big tech company to enter the mix with its recently announced *Series 4 Apple Watch*, the first smart watch with integrated electrical sensors and FDA-cleared AF detection algorithms capable of producing a 30-second ECG when the user touches the Watch's crown. (*See "Digital Technologies Shake Up Arrhythmia Monitoring, Part 1: Apple's New ECG-Enabled Watch—Gizmo or Game Changer?"* MedTech Strategist*, September 28, 2018*.)

Apple's new ECG-enabled Watch is a potential game-changer in this field because it opens up AF screening to a huge and diverse consumer population, most of whom, presumably, are at low risk for AF. As such, it could provide some much needed data on the benefits and drawbacks of widespread AF screening in the asymptomatic patient population. However, it also has some important limitations.

Figure 1

The $1.4B US Ambulatory Arrhythmia Monitoring Market



Source: iRhythm; Frost and Sullivan

Figure 2

Selected Competitors with Wearable Digital and AI-Based Arrhythmia Monitoring Technologies

Company/Product	Status	Comments
AliveCor* *KardiaBand* ECG sensor-enabled wrist band for Apple Watch and associated AI-enabled app. Combines data input from ECG, heart rate, and activity sensors and uses machine-learning AI to detect abnormal rhythms indicative of AF	FDA cleared in November 2017 and sold direct-to-consumers online	First medical-grade ECG band designed for use with Apple Watch and first FDA-approved AI algorithm to aid in collecting consumer data for a medical diagnosis
Apple* The new *Series 4* Apple Watch has PPG (photo-plethysmograph) and ECG sensors plus FDA-cleared software applications to detect AF. Company is also collaborating with Stanford University researchers to conduct the 500,000-patient Apple Heart Study for AF detection with older models of its Watch using only PPG monitoring. Study participants who experience an irregular heart rhythm receive a free telehealth consult through **American Well** and, if needed, a free *e-Patch* heart monitor from **BioTelemetry Inc.** (formerly CardioNet); *e-Patch* is a small, body-worn sensor that continuously records and stores 1-3 channel ECGs for up to 72 hours	*Series 4* Watch was launched in September. AF detection apps will launch later this year	The Apple Heart Study was launched in November 2017 and enrollment was closed to new participants on August 1, 2018. The study will reportedly continue at least through the end of this year
Cardiac Insight* *Cardea SOLO* Wearable sensor continuously records up to 7 days of beat-to-beat ECG data. After the monitoring period, the data stored in the device is analyzed, and a report prepared, right in the physician's office	FDA cleared April 2017	This is a device-based, versus a service-based, business model
Cardiac Monitoring Service (CMS) Company's new *myPatch SL* Holter monitor is a small, single-electrode device that can be easily adhered to the chest (the short electrode is placed on the upper sternum). It can record 1-2 channel ECGs for up to 14 days and 3-channel ECGs for up to 9 days and is shower proof. When monitoring is complete, it is plugged into a computer in the physician's office via a USB cable. The data is uploaded to a secure, online portal, analyzed by certified technicians, and an online report is generated	On US market	CMS has been providing arrhythmia monitoring equipment and services for more than 20 years and claims over 4,000 physician clients nationwide
CardiacSense* (Caesarea, Israel) Company is developing a smart watch that incorporates proprietary optics and algorithms to continuously monitor for AF	Clinical study for FDA clearance and CE mark to begin soon. Hopes to have FDA clearance by mid-2019	Watch uses PPG and ECG sensors and incorporates proprietary motion noise filters; it communicates with mobile app that sends report to physician. Initial clinical study showed sensitivity and specificity of more than 97%
Cardiogram Developing machine learning algorithms for the detection of AF on a smart watch by analyzing PPG blood flow signals	In development	Study published this year in *JAMA Cardiology* showed only 68% sensitivity and specificity for the algorithm in an ambulatory patient cohort—an accompanying editorial called the results "humbling" when compared with gold-standard ECG

Cardiologs *Cardiologs ECG Analysis Platform* Cloud-based AI software service for analyzing ECGs from any compatible digital monitoring device	FDA cleared July 2017	Company claims positive predictive value of 91% for AF and sensitivity of 97%—which it says provides the highest diagnostic yield with the least physician effort
InfoBionic* *MoMe Kardia* mobile cardiac monitoring system Patient-worn device that can operate in Holter, Event, or MCT mode, and Cloud-based SaaS platform with deep-learning algorithms. Device wirelessly streams beat-to-beat data to the Cloud via cellular network and software provides near real-time physician access to the data as well as automated reports on demand	FDA cleared March 2016	Largely a service-based model. Aim is to reduce time to diagnosis and intervention; simplify the process for physicians, patients, and payors; and enable physicians to bill for both the technical and professional components Company reported nearly 600% year/year growth in both new customers and annual recurring revenue in 2017
iRhythm Technologies* *Zio XT* patch & associated *MyZio* smartphone app Small patch is adhered to chest; captures beat-to-beat, single-channel ECG data continuously for up to 14 days; records both patient-triggered and asymptomatic events 24/7. Patient mails back device and company uses machine-learning algorithm to analyze results. Report is then issued to physician *Zio AT* – has all the features of *Zio XT*, including beat-to-beat continuous data collection for up to 14 days, plus real-time detection, transmission, and notification of clinically actionable arrhythmias. Generally indicated for patients with symptoms suggestive of high-risk arrhythmias. This is iRhythm's entry into the MCT (mobile cardiac telemetry) space	*Zio XT* on US market since 2011 *Zio AT* FDA cleared in June 2017	Founded in 2006, iRhythm pioneered the patch-based continuous ECG monitoring space. Company reported revenues of $98.5 million in 2017, an increase of 54% year/year. Company claims approx. 10% share of the symptomatic arrhythmia monitoring market
Peerbridge Health Inc. *Cor* Wearable, leadless, 2-channel ECG monitor with Bluetooth connectivity and patient-activated event button. Captures and transmits continuous ECG info and symptomatic events for 24 hours up to 7 days. Data transmitted to and analyzed by Cloud-based algorithms	FDA cleared October 2017	Company claims smallest on-body footprint for leadless multichannel wearable. *Cor* can provide Holter, Event, and Extended Holter (up to 7 days) tests. Head-to-head study comparing *Cor* with standard Holter monitoring found *Cor* was superior in terms of ECG quality

Source: *MedTech Strategist*

*Related Reading:

AliveCor: "Digital Health: What's Hot, What's Not," MedTech Strategist*, January 31, 2018*

Apple Watch: "Digital Technologies Shake-Up Arrhythmia Monitoring, Part 1: Apple's New ECG-Enabled Watch—Gizmo or Game Changer?" MedTech Strategist*, September 28, 2018*

"Cardiac Insight: Upending the Mobile Cardiac Monitoring Business," MedTech Strategist*, May 31, 2017*

CardiacSense: See sidebar "CardiacSense: A New Watch Competitor in the Wings," this issue

"InfoBionic: Set to Disrupt Arrhythmia Monitoring," MedTech Strategist*, August 24, 2016*

iRhythm: "The 'Smart Healthcare' Revolution: Can Digital Tools, Advanced Biosensors, and Data Analytics Transform Healthcare as We Know It?" MedTech Strategist*, December 6, 2016 and "Wearable Technologies: What's in it for Medical Device Companies?"* MedTech Strategist*, March 16, 2016*

It is not intended to provide a diagnosis, rather it simply tells the user if their ECG "shows signs of Afib." Thus it will not replace the need for more definitive, physician-directed diagnostic monitoring with devices such as those from iRhythm. In fact, iRhythm could actually see an increase in demand for its *Zio* continuous 14-day ECG patch as a result of the Apple Watch's wider reach. Moreover, unlike *Zio* and other existing ECG monitoring devices, Apple's new Watch and algorithms are not designed to detect arrhythmias other than AF (at least for now), which limits the Watch's overall utility as an arrhythmia monitoring device. Perhaps most importantly, Apple is a newbie in the healthcare space. Although there's no doubt its phones, watches, and apps can engage young, well-heeled consumers, just how well Apple will do when it comes to helping people recognize and manage serious health conditions such as AF remains to be seen.

That said, since suspected AF is one of the most common reasons people undergo ambulatory arrhythmia monitoring, some existing ECG technologies could definitely feel Apple's impact. One company in particular that is likely to be adversely affected by Apple's new Watch is **AliveCor Inc.**, which last November received FDA clearance (as a medical device accessory) for its *KardiaBand*, a sensor-enabled watch band for previous versions of the Apple Watch that enables users to take a 30-second ECG simply by touching the watch band. (*See "Digital Health: What's Hot, What's Not,"* MedTech Strategist, *January 31, 2018*.) Although it is possible in the coming months that growing public awareness of ECG monitoring, thanks to Apple's recent launch, could drive more people to the *KardiaBand*, which sells for $99 online (discounted recently from $199), that is likely to be only a temporary boost for AliveCor, since it's only a matter of time before Apple stops supporting older versions of the Watch and users are forced to upgrade for full functionality.

AliveCor also offers *KardiaMobile*, an FDA cleared mobile ECG touch pad and app for AF detection that is compatible with both iOS and Android smartphones and tablets. And the company is leveraging its technology beyond AF as well. In September, AliveCor announced that it had received FDA breakthrough device designation for a new software platform called *KardiaK*, which noninvasively screens ECG data to detect elevated levels of blood potassium (hyperkalemia). Hyperkalemia is common in patients with kidney disease and can be life-threatening. The new algorithm was developed using data collected from more than two million ECGs that were linked with four million serum potassium values. The company is also working with Mayo Clinic to develop an AI algorithm that can identify people with congenital long QT syndrome (LQTS) who have a normal QT interval on a standard ECG. LQTS patients are at increased risk of arrhythmia and sudden cardiac death, but according to the company, up to 50% of those with genetically confirmed LQTS have a normal QT interval on a standard ECG and thus may go undiagnosed. Researchers from Mayo presented promising results from the collaboration at the Heart Rhythm Society meeting this May, noting that the algorithm was built by looking only at data from lead 1 of a 12-lead ECG, which suggests that the single-lead information from mobile ECG devices such as *KardiaMobile* and *KardiaBand* may one day be able to screen for this condition.

Implantables Face Growing Competition

AliveCor is likely to feel the initial brunt of Apple's entry into AF monitoring, but others could be impacted as well. Some observers believe implantable loop recorders also could experience some pressure from the new Watch, in large part due to the cost differential: ICMs cost several thousand dollars to implant while prices for Apple's *Series 4* Watch start at $399. Although there are patients who will remain ideal candidates for an implantable monitoring device (e.g., older, less tech-savvy people who are at high risk of a stroke or other adverse event and who require long-term monitoring for AF or another, even higher-risk, arrhythmia), others might do just as well using the Watch as an initial AF screening tool and following up, if problems are detected, with a diagnostic wearable like *Zio*.

ICMs represent the smallest segment (about 2%) of the total ambulatory cardiac monitoring market; however, their use has been expanding of late, driven by the introduction of advanced, digitally connected offerings and by positive reimbursement trends. Medtronic led the way in this regard with its *Reveal LINQ* ICM, which has been on the US market since 2014 and is widely covered. Smaller than a triple-A battery, *Reveal LINQ* is inserted under the skin of the chest through a 1-cm incision. The device monitors ECG heart rhythms for up to three years (projected battery life), automatically detects and records arrhythmia events, and wirelessly transmits the data to Medtronic's *Carelink* network via a bedside monitor.

Medtronic has been a dominant force in the implantable loop recorder segment for several years, but the company is now facing growing competition from other big medtech players, including **Abbott Laboratories Inc.** and **Boston Scientific Corp.**, as well as from tech companies like Apple.

Abbott entered the ICM space last fall with its *Confirm Rx* device (developed by St. Jude Medical, which Abbott acquired in 2016), and Boston Scientific is expected to have an ICM on the market sometime in 2019. Abbott's *Confirm Rx* ICM has a projected battery life of two years, compared to Medtronic's three-year life, but Abbott's device is the first ICM that is smartphone compatible—no handheld activator or bedside transmitter is required, which is a plus for many patients. The device uses Bluetooth to connect to the patient's smartphone via the *myMerlin* mobile app. The data collected is transmitted proactively to the patient's physician based on a prearranged schedule and is also stored on the

company's Merlin.net site for physician review. In addition, patients can record and send tracings of symptomatic events to their physician and can annotate those events to describe their symptoms. Abbott also claims that *Confirm Rx*, at 14 cc and 3.1 mm thick, is the "slimmest" ICM on the market today. Abbott says US sales of *Confirm Rx* have been strong since the launch last fall; during the second and third quarters of 2018, the company noted that growth in its electrophysiology business was led in part by sales of *Confirm*.

Medtronic also has posted strong growth in its *Reveal LINQ* business over the past several years; however, that momentum slowed in recent months due to competition from Abbott. During Medtronic's Investor Day meeting in June, company executives noted that Abbott was pricing *Confirm Rx* at about a 10% discount, which boosted Abbott's launch momentum. Still, Medtronic management said it is confident the company will be able to regain lost share due to *Reveal LINQ*'s "better accuracy" and longer battery life, according to Larry Biegelsen, senior analyst with Wells Fargo Securities. In terms of accuracy, last year Medtronic received FDA clearance for *Reveal LINQ* with *TruRhythm* Detection, which includes updated algorithms designed to improve accuracy. The company says the new algorithms can learn a patient's normal heart rhythms and thereby decrease the rate of AF false positives by 49%.

Despite its claims of superior accuracy, Medtronic is likely to continue to feel the competitive pressure until the release of its next-generation *LINQ II*, which is slated for launch in the FY 2019/2020 timeframe (no later than April 2020 on the calendar). *LINQ II* will feature a wafer scale footprint, a five-year battery life, improved accuracy, a smartphone interface with Bluetooth connectivity, and vital signs sensors, and it may be eligible for additional indications in chronic disease management, including AF in heart failure patients and arrhythmias associated with end-stage renal disease. According to Jason Mills, an analyst with Canaccord Genuity, with the new, longer-wear *LINQ II* platform, Medtronic "is focused on bringing pricing down for its ICM" to a level that is more competitive with external long-term continuous wear monitoring devices (e.g., iRhythm's *Zio* patch).

While *LINQ II* moves through the pipeline, Medtronic is taking other steps to consolidate its position in this space. In May, the company announced it would stop selling its *SEEQ* 30-day wearable mobile cardiac telemetry patch, a decision that takes Medtronic out of the MCT segment altogether and enables it to focus solely on *Reveal LINQ* and the ICM market. Medtronic obtained the *SEEQ* patch when it acquired Corventis in 2014 for about $150 million. Medtronic tells *MedTech Strategist* that the decision to stop selling *SEEQ* was aimed at directing growth to "areas where [the company] can deliver the most meaningful innovation and value for patients and healthcare providers." The short-term arrhythmia monitoring market has "changed significantly in a short period of time," the firm said in an emailed statement, "with many companies offering similar technologies. We believe we can best help our customers transform patient care by further investing in our highly differentiated *Reveal LINQ* ICM solution." *SEEQ* was marketed in the US, Mexico, Colombia, and Saudi Arabia and represented "a very small portion of business for Medtronic," the company noted, adding that Medtronic plans to "continue to invest" in cardiac monitoring and diagnostic technologies. The news is a net positive for iRhythm, according to Canaccord Genuity analyst Jason Mills, who noted in a June 6 Industry Update that the decision by Medtronic to discontinue *SEEQ* offers "further validation of *Zio*'s differentiation in the ambulatory ECG market and [iRhythm's] strong competitive positioning."

iRhythm's Success Drives Interest in Digital Wearables

The fact that Medtronic sees competitive threats coming not only from new ICMs but also from digital external-wear devices is a testament to the growing popularity of new, more patient-friendly arrhythmia monitoring wearables. And to date, no company has been more successful with a wearable in this space than iRhythm, with its *Zio* patch, a wireless, *Band-Aid*-like ECG sensor patch that can be worn on the chest continuously for up to 14 days. *Zio* records and stores beat-to-beat ECG data for the entire wear period and enables patients to flag an event if they feel symptoms. When the monitoring period is over, the patient simply mails the device back to the company and the stored data is uploaded to iRhythm's Cloud-based server where it is analyzed using proprietary AI-driven algorithms to identify any key arrhythmias. A report is then generated and made available to the patient's physician, typically within 24 hours of the data upload.

As a 14-day wearable patch, the *Zio* is quite a departure from traditional Holter monitors, which as mentioned, are bulky devices that require multiple wired electrode leads adhered to the patient's chest. Unlike the *Zio*, traditional Holter devices must be removed for showering, are difficult to hide under clothing, and can be problematic to wear during sleep and exercise. As a result, patient compliance issues and gaps in data collection are commonly cited problems with these devices that can impact diagnostic yield. According to iRhythm, traditional Holter monitors have demonstrated a relatively low diagnostic yield of only about 24%, in part due to data gaps that occur when patients remove them to shower, sleep, and exercise.

But perhaps the biggest drawback to traditional technologies is their limited data collection capability. Traditional Holter monitors are only able to collect continuous ECG data for a maximum of 48 hours, and thus are largely ineffective when it comes to catching rarely occurring arrhythmias, including

paroxysmal (transient) AF. In fact, recent studies have repeatedly shown that newer technologies capable of longer ECG monitoring times (one week or more) catch significantly more cases of paroxysmal AF than traditional Holter monitors.

Changing the Paradigm

The *Zio* patch was designed to address the limitations of traditional Holter devices. iRhythm's flagship device, the *Zio XT*, was FDA cleared in 2011, and after several years of effort by the company to gain payor coverage is now covered by the majority of US insurers. According to Derrick Sung, EVP of Global Strategy and Corporate Development at iRhythm, more than 90% of insurable lives in the US—over 290 million people—now have access to the device through their private or public health insurance.

The fact that iRhythm was ultimately able to obtain such widespread payor buy-in for *Zio*—the first wearable, digital solution in a highly fragmented, but well entrenched, market—speaks as much about the company's tenacity and execution (and its ability to maintain sufficient financial support over its now 10+ year lifetime) as it does about the technology itself. But iRhythm's remarkable success in this space—measured not only by its claimed 10% market share, but also by the growing number of would-be imitators—also points to the technology's ability to successfully fill a substantial unmet need.

According to Sung, the *Zio XT* addresses 90% of the mobile arrhythmia monitoring market—including both the continuous Holter monitor and event monitor segments. And the device's 14-day continuous monitoring capability is what differentiates it in both segments of the market. He points to a number of clinical studies that he says have demonstrated the advantages of having continuous, beat-to-beat data collected over an extended two-week period—benefits that include "significantly higher diagnostic yield—three to four times higher than a Holter monitor," earlier diagnosis of critical events, and a reduced need for repeat monitoring.

The company is now leveraging those benefits to expand its reach into the remaining 10% of the market it hasn't served before—the mobile cardiac telemetry segment. Here again, iRhythm aims to disrupt the space with its new *Zio AT*, which was FDA cleared in June 2017. The *Zio AT* delivers all the functionality of the *Zio XT* with the addition of mobile telemetry capability, which provides near real-time detection, transmission, and notification of clinically actionable arrhythmias. It is aimed at the relatively small subset of patients with symptoms suggestive of high-risk arrhythmias—for example, unexplained loss of consciousness (syncope) that might be due to ventricular tachycardia—that require immediate notification and rapid intervention.

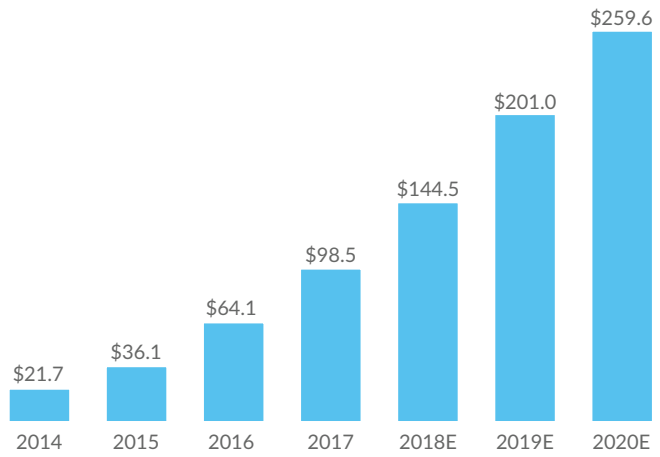
iRhythm believes the *Zio AT*'s unique combination of near real-time telemetry and 14-day extended, continuous monitoring capabilities gives the company a unique competitive edge in the MCT space. "We approached the [MCT] market from the perspective of *Zio XT*," notes Sung, who says the demonstrated value of beat-to-beat monitoring translates directly to the MCT market and provides a "unique differentiating factor" for the company in the MCT segment. There's a "clear market need" for this capability in MCT, he adds, "and it fills in a strategic piece of our portfolio." With the *Zio AT*, iRhythm has the final piece (mobile telemetry) that will enable it to address the entire space, Sung asserts.

iRhythm has experienced strong growth over the past several years as *Zio* has steadily gained market share. The company's revenues grew from about $36 million in 2015 to nearly $100 million last year and are on track to reach more than $250 million by 2020, according to Jason Mills (*see Figure 3*). In a September 12 note, Mills said he views Apple's entry into AF monitoring as "a potential market expander" for *Zio*, "as wearable devices further highlight the benefit of prophylactic monitoring, helping funnel patients into physicians' offices" for confirmatory testing with longer-term continuous ECG monitoring devices. "We continue to believe [iRhythm] has built and continues to advance a platform that is actively changing the paradigm in ambulatory ECG monitoring," he added.

Some 4.5 million cardiac ambulatory monitoring tests are performed annually in the US—the majority for diagnosis of symptomatic arrhythmias. And iRhythm sees "significant opportunity" to grow the market in new areas, such as ambulatory monitoring of asymptomatic high-risk patients, Sung points out.

Figure 3

iRhythm Global Revenue Forecast, 2014-2020E ($M)



Source: Jason Mills, Canaccord Genuity, October 2018

Meanwhile, the company has been ramping up its commercial sales force and working to drive awareness. iRhythm has more than doubled its sales force over the past two years, according to Sung, who says that has been a major contributor to growth. Going forward, increased awareness, driven by "feet on the street and continued clinical acceptance" will be an important component of near-term growth, he adds, as expanding clinical evidence continues to drive "growing awareness of *Zio XT* as a gold-standard of care."

A Big Data Play

One thing iRhythm has going for it is a growing wealth of clinical data on the *Zio* technology. One recently published study of note is the KP RHYTHM trial, which used the *Zio XT* to look at the impact of AF burden (the percentage of time people spend in AF) on stroke risk. KP RHYTHM looked specifically at people with paroxysmal AF who were not taking anticoagulant drugs (a population "for whom decisions about stroke prevention strategies can be challenging," the study authors note). In this five-year retrospective study, conducted by Kaiser Permanente and published in May in *JAMA Cardiology*, researchers analyzed data from nearly 2,000 patients who had been monitored with *Zio* and were found to have paroxysmal AF, looking specifically at their AF burden. They found that a higher AF burden was independently associated with a higher risk of ischemic stroke or other thromboembolic event and the risk was more than three-fold higher in people with the greatest AF burden.

The study does come with some caveats and is not robust enough to modify current practice guidelines, according to Fred Morady, MD, who wrote a summary of the findings for the American College of Cardiology. However, it adds to the growing awareness of AF burden among the physician community; the American Heart Association issued a Scientific Statement earlier this year acknowledging the importance of AF burden as an indicator of stroke risk. And iRhythm, which sponsored the KP-RHYTHM study, appears to be in a unique position to benefit in the marketplace from this trend—its back-end analytics technology provides a *True AF burden* calculation for every patient monitored with *Zio*.

KP-RHYTHM is just one of several studies that are matching *Zio*-collected data with other large data sets, such as the Kaiser patient data base, according to Judy Lenane, iRhythm's EVP of Operations and Chief Clinical Officer. Lenane says the company is "looking at the whole realm" of information to better understand how to identify AF patients who are at high risk. "We have more than 300 million hours of curated ECG data," she points out, and are partnering with others to analyze and understand this data, with the ultimate aim of "creating better tools." This is "rich data," she adds, and shows "what AF looks like in the real world."

Leveraging its data in this way has distinct economic and competitive advantages for the company, says Derrick Sung. "If we had wanted to conduct [the KP-RHYTHM] study prospectively," he explains, "it would have taken years to analyze clinical outcome rates because stroke has a very low incidence [in this patient population]. That's another advantage that we have with our database, to be able to do these types of studies and demonstrate the clinical utility of our products."

As for utilizing its vast data trove to create better tools, iRhythm recently partnered with researchers at Stanford University's Machine Learning Group to develop a deep-learning algorithm that was trained on a roughly 30,000-patient annotated ECG data set the company collected. According to the researchers, the resulting algorithm—a "34-layer convolutional neural network comparable to AI models used in computer vision and speed recognition"—is capable of "expert level classification" of 14 different arrhythmias, including AF, atrial flutter, complete heart block, second-degree AV block, and ventricular tachycardia. When tested against six cardiologists, the algorithm outperformed the physicians on diagnosing most arrhythmias, according to the Stanford team, which believes the algorithm could one day be incorporated into a wearable device that would alert emergency services if the user experienced a life-threatening arrhythmia.

Branching Into Asymptomatic Screening

In addition to making use of its growing mass of ECG data, iRhythm and others with digital monitoring technologies are also helping transform the way clinical trials are run by providing tools that enable a more pragmatic, real-world approach to clinical research than has been possible in the past. One recently published trial is of particular importance in this regard: the investigator-initiated, randomized mSToPS study. mSToPS is one of the first large, remotely run clinical trials enabled by digital, wearable monitoring technology, and it is notable for its home-based, direct-to-participant design, aimed at generating as close to real-world data and outcomes as possible. (*Editor's Note: We'll have a detailed discussion of mSTopS, and the implications for future clinical trial designs, in a future issue when we interview mSToPS principal investigator, Steven Steinhubl, MD.*)

Conducted by researchers at the Scripps Translational Science Institute in San Diego, in collaboration with US insurer **Aetna Inc.**, mSToPS enrolled more than 2600 people across the US who were identified from Aetna claims data as being at high risk for AF. All participants were remotely enrolled and instructed—no clinic visits were required and all monitoring was done remotely using the *Zio* patch, which participants mailed back to the company for analysis. The study was undertaken to determine, in a real-world setting, whether a wearable ECG device is more effective than routine care at detecting undiagnosed AF in high-risk individuals. The study will follow patients for three years to look at clinical outcomes and cost effectiveness, but the primary outcome results, published in *JAMA* in July, found that monitoring with *Zio* identi-

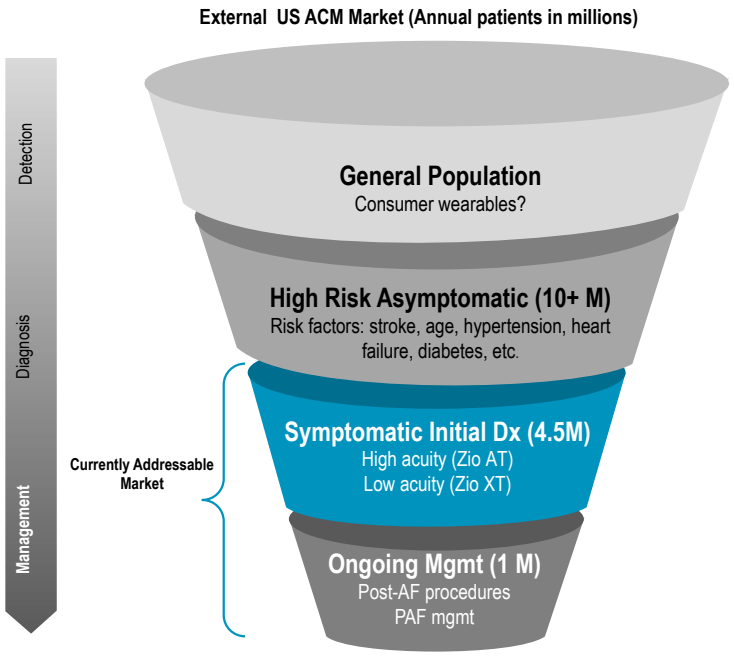
fied significantly more AF over a four month period than did routine care (3.9% vs. 0.9%).

iRhythm hopes to leverage the mSToPS data, as well as evidence from additional trials currently planned or ongoing, to expand *Zio* utilization among asymptomatic individuals who are at high-risk for AF, an opportunity the company estimates would add millions more people to the potential *Zio* patient pool (*see Figure 4*). "There's growing interest in the clinical community, as well as the payor community, to explore this notion of earlier diagnosis through targeted detection using ambulatory monitoring with devices like the *Zio XT*," notes Sung. The ultimate aim is to treat patients earlier in order to reduce future events like stroke, which not only could have a profound clinical impact, but also could save the system a lot of money, he adds. "That's why we're involved in conducting studies to develop that evidence."

In addition to mSToPS, there is a similar study—SCREEN-AF—underway in Canada and Germany that could complete enrollment later this year. But iRhythm is not alone in this effort—others, including Apple, are leveraging arrhythmia wearables and other digital technologies as a means to conduct remote, pragmatic clinical trials in large patient populations. And it's only a matter of time before these efforts yield data that can help inform, and potentially grow, this market.

Figure 4

Total Addressable Market for Ambulatory Cardiac Monitoring



Source: iRhythm; Frost and Sullivan

USPSTF: Evidence for Screening Insufficient

iRhythm already has broad FDA labeling for *Zio* for use in both symptomatic and asymptomatic cases; however, the vast majority of current use falls into the symptomatic category since the benefits of AF diagnosis and treatment (anticoagulant therapy) in this group are well-established. Expanding into the asymptomatic population is likely to be an uphill battle with payors, although progress is being made. According to researchers, about 10% of ischemic strokes occur in people who are first diagnosed with AF at the time of the stroke, and it is hoped that many of those strokes could be prevented by widening AF screening programs to high-risk, asymptomatic individuals. mSToPS is just one of several studies underway or planned to gather data on the risks and benefits of more widespread AF screening programs, but at present the evidence for or against such an approach is scarce.

The dearth of existing data on the benefits of ECG screening for AF, even in high-risk populations, was highlighted earlier this year when the US Preventive Services Task Force (USPSTF), whose recommendations are often used to help guide not only clinical adoption but payor coverage decisions as well, issued a new recommendation statement on this topic, noting there isn't yet enough clinical evidence to determine the net benefit of ECG screening in older, asymptomatic adults (age 65+).

The recommendation statement, published in August in *JAMA*, was based on a review of 17 studies involving more than 135,000 patients. Although the studies demonstrated that ECG screening can detect previously undiagnosed cases of AF in people without noticeable symptoms, the reviewers noted there is no published evidence yet demonstrating that routine screening with ECG is better than standard intermittent screening with pulse palpation, nor is there adequate data showing that routine ECG screening has a positive effect on clinical outcomes. No trials have yet assessed whether treating asymptomatic AF patients identified by ECG screening results in better health outcomes compared with treatment following detection by usual care or after symptoms develop, they said. Bottom line: the agency concluded there isn't enough evidence to determine whether or not AF screening and subsequent treatment in asymptomatic adults is more effective than usual care or to assess whether the benefits of ECG screening in this population outweigh the potential harms.

According to the USPSTF, screening that results in false positive diagnoses leads to some of the most serious potential harms. In one study of 12-lead ECG tracings, for example, general practitioners misinterpreted 8% of normal sinus rhythm cases, instead diagnosing them as AF, and they missed 20% of actual AF cases.

Patients mistakenly diagnosed with AF could be subjected to unnecessary treatment with anticoagulant drugs, which would elevate their risk of bleeding, and/or unnecessary invasive follow-up testing/treatment.

The Task Force members, along with several other physicians who commented on the recommendation paper, also noted there are a number of important knowledge gaps that still need to be addressed when it comes to AF screening and treatment. Clinicians don't yet have a full understanding of the actual stroke risk associated with brief episodes of subclinical AF, nor is there a clear consensus on how to treat these patients, they point out. mSToPS, along with several other ongoing and upcoming studies, should help answer some of these lingering questions; in fact, it is quite possible that will prompt USPSTF to revisit this topic two or three years down the road. Interestingly, several physicians have also pointed to the potential for consumer-based wearables, such as Apple's new Watch, to aid in this data collection effort.

Steven R. Steinhubl, MD, of the Scripps Translational Science Institute, who was the principal investigator for mSToPS, believes we could soon approach a turning point in terms of gathering clinical evidence on the benefits, risks, and costs of ECG screening in targeted (i.e., high-risk) asymptomatic populations. "We've had several decades of very little movement on screening at all," says Steinhubl, "but our understanding of AF—it's prevalence, risk factors, what we can do when we find it, and who should and shouldn't be anticoagulated—is going to increase very quickly over the next few years."

A Crowded Space Becomes a Digital Health Proving Ground

Meanwhile, the list of competitors and technologies in this space continues to grow. Several new and existing competitors now offer, or are developing, more patient-friendly wearable or even handheld monitoring devices, with many hoping to repeat, or at least benefit from, iRhythm's success. (Of note in the handheld ECG category are the *MyDiagnostick* device from **Applied Biomedical Systems BV**, which is being used in the IDEAL-MD AF screening study; the *imPulse* thumb device from **Plessey Semiconductors**, which will be used in an NHS-sponsored AF screening study scheduled to begin in the UK this year; and the *Zenicor-ECG* from **Zenicor Medical Systems AB**, another thumb-based handheld being tested in the 8,000-patient STROKESTOP asymptomatic AF screening registry study ongoing in Sweden.)

But iRhythm's Derrick Sung cautions the task—at least for those developing patch-based devices—is not that simple. In fact, the company believes the barriers to entry are actually quite high. Given iRhythm's success, "it's no surprise to us that we see folks trying to follow in our footsteps," he says, but "we think we have a significant, multi-year lead with high moats around our businesses."

The first hurdle is replicating a patch that can stay on the body and monitor continuously, on a beat-to-beat basis, for up to 14 days, which is "no small feat," says Sung, who also points out that iRhythm has "a lot of IP protection" around its patch technology. Assuming a competitor scaled that technical hurdle, they would then run into the challenge of how to process the one-and-a-half to two-million heartbeats worth of ECG data that the device would collect, he adds. "It's probably half a gig of data—30,000 to 40,000 pages of ECG data if it were printed out on traditional ECG paper. And that's where I think a lot of our secret sauce lies—in our back-end analytic platform."

Through its Cloud-based, AI-driven algorithms, iRhythm can analyze the full 14 days-worth of data in "an efficient and cost-effective manner," Sung says. "And to get there, we not only had to develop our own proprietary machine learning, AI-driven algorithms, but we also had to gather the data, because the AI algorithms require massive amounts of data in order to be trained." iRhythm now has a database of well over a million patients, he points out, and "it took us a good 10 years and $120 million or so in venture investment" to reach that point. During that time, the company also worked to collect the clinical evidence and put the reimbursement component and workflow tools into place, additional hurdles for would-be competitors. "So if you put it all together, it's a complete system, and I will tell you that it's not very easy to replicate," Sung asserts.

Tech companies such as Apple and Google could have an advantage when it comes to developing the necessary algorithms, and the data Apple will be able to collect with its new Watch presumably will be a key component driving the evolution of its system going forward. But, as mentioned, at least for now, the Apple Watch will not provide a definitive diagnosis, so any issues picked up by the Watch are likely to only increase demand for *Zio* and other existing ECG diagnostic devices.

Of course, that could change as the field evolves and consumer-focused wearables like Apple's Watch improve and potentially expand their capabilities. Indeed, there is already one start-up with a competitive smart watch in late-stage development: Israel's **CardiacSense** believes its watch will be FDA cleared as a diagnostic for AF, which would be a substantial advance over Apple's current offering (*see Sidebar "CardiacSense: A New Watch Competitor in the Wings"*).

Exactly how this all plays out in the months and years ahead is anyone's guess at the moment, but it is clear that arrhythmia monitoring is poised to be an important proving ground for the future of digital health technologies. And although there are likely to be some bumps along the way, the ultimate impact of this transformation could be far-reaching—not only providing a roadmap for future efforts in patient-centric care and pragmatic clinical trial design, but also offering a glimpse of the potential risks and rewards likely to occur when digital consumer technologies and healthcare converge.

CardiacSense: A New Watch Competitor in the Wings

As the ambulatory arrhythmia monitoring field evolves, consumer-focused wearables like **Apple Inc.**'s *Series 4* Watch are likely to improve, possibly to the point where they can provide a diagnostic result, a development that would increase competitive pressure on existing diagnostic technologies like iRhythm's *Zio*. In fact, one start-up targeting this space is already working toward FDA diagnostic labeling for its arrhythmia monitoring smart watch. **CardiacSense**, based in Caesarea, Israel, will soon begin a pivotal clinical study with its watch that will support both FDA clearance and CE marking for the device as a diagnostic tool for atrial fibrillation *(see Figure 1*). That puts it a step ahead of the Apple Watch's new AF detection algorithms, which are not labeled for diagnostic use.

According to Amnon Blanca, head of Business Development for CardiacSense, the company has developed a smart watch that utilizes both PPG and ECG signals and that incorporates a proprietary Artifact Sensor to address arm movement, which he calls "the Achilles Heel of PPG." The device is a complete diagnostic system, he says, including an algorithm plus special optics and mechanics in the watch itself. "We do something that nobody else does," he asserts, "and it's all IP protected" (the company has filed 10 patents and four have been issued). The company's Artifact Sensor is a motion noise filter that can "recognize any sort of movement," says Blanca, which is what differentiates the firm's technology from the Apple Watch. "When you move your arm, the accelerometer on your smart watch will recognize the movement," he explains. "But what happens when you move your fingers or your palm without moving your arm? The PPG signal is going to go crazy, but the accelerometer won't recognize that movement. Our Artifact Sensor can also recognize this movement," he says, adding that the company has achieved high levels of accuracy for AF (more than 97%) in preliminary studies and is preparing to begin its official ambulatory clinical trial.

Figure 1

CardiacSense's AF Monitoring Smart Watch

Source: CardiacSense

CardiacSense hopes to obtain FDA *de novo* clearance for the watch as an AF diagnostic by mid-2019. The company is also planning other applications for its watch technology, including continuous blood pressure monitoring, and detection and emergency notification of cardiac arrest. The company's eventual vision is to have a watch that provides "all the vital signs necessary for monitoring a person," Blanca says. Moreover, the data it will collect will "enable us as watch developers, and most importantly, as the data keepers, to go from sickness management to health management."

Initially founded in 2009 as consumer health company SportTracker (it rebranded as CardiacSense about four years ago), CardiacSense is a portfolio company of Merchavia Holdings & Investments Ltd. To date, the company has raised nearly $5 million from Merchavia as well as angels and other private investors. And, it has a partnership with Cleveland Clinic, which Blanca says is working with the firm on its business model and will be involved in a post-market US clinical trial of the watch.

When asked if the company has any trepidations about going up against tech giant Apple in the marketplace, Blanca admits that it won't be simple. "But we are very confident in our technology and our IP," he asserts, adding that the firm will compete directly with Apple if need be, but "we will not go head-to-head with Apple by ourselves." CardiacSense intends to partner to bring its technology to mar-

ket, but its first choice is not, as some might assume, an Apple rival in the consumer smart watch space (although it wouldn't refuse such a collaboration if offered, says Blanca). Rather, the company hopes to partner with a large medical device firm, preferably one that is already operating in the arrhythmia monitoring market.

To understand that reasoning, you need only consider what Apple is facing going forward, Blanca explains. "Apple is not a player in the medical arena—you need a connection to the hospitals, you need to work with physicians. They're not in this domain; it will take them a long time. But if our technology works and we team with a company that is already operating in this space, the go-to-market is much shorter." (Interestingly, Apple appears to be pushing into the medical arena at a surprisingly rapid pace. Not only is the company working with Stanford University researchers on Apple Watch-based arrhythmia monitoring, but it recently announced a collaboration with orthopedic implant company **Zimmer Biomet Inc.** to conduct a 10,000-patient clinical study of Zimmer's new *mymobility* app for the Apple Watch. The app tracks patients following hip and knee replacement surgery, collecting both patient-reported feedback and continuous health and activity data from the Watch.) (*See also "Do Wearables Have a Medical Role in Orthopedics?" this issue.*)

"We're in an interesting time," notes Blanca, "because consumer electronics and medical are starting to overlap. That's why Apple is interested—it's a huge market. But the medical arena is lagging behind the consumer space in accepting new technologies—it's moving slowly. And it's easier to adopt a new product through existing channels."

That said, Blanca is appreciative of the attention Apple is bringing to the arrhythmia monitoring space. Apple's launch of the *Series 4* Watch "did only good things for us," he says. "Because now that Apple is [getting into this field] there's no question about the market or the need. We only need to show that we do better than Apple, and we know for a fact we are doing better than them."