Remote and Wearable ECG Devices with Diagnostic Abilities in Adults: A State of the Science ~~Narrative~~ Scoping Review

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ABSTRACT

The electrocardiogram (ECG) records the electrical activity in the heart in real-time, providing an important opportunity to detecting various cardiac pathologies. The 12-lead ECG ~~simultaneously acquires the electrical signal from several spatial directions, enabling the assessment of the heart in a three-dimensional model and, thus, making it the~~ currently serves as the "standard" ECG acquisition technique for diagnostic purposes ~~tool~~ for ~~most~~ many cardiac pathologies other than arrhythmias. However, the technical aspects of acquiring a 12-lead ECG are not easy and its usage is currently restricted to trained medical personnel, limiting the scope of its usefulness. Remote and wearable ECG devices have attempted to bridge this gap by enabling patients to take their own ECG using a simplified method at the expense of a reduced number of leads, usually a single-lead ECG. In this review article, we summarize the studies which investigate the use of remote ECG devices and their clinical utility in diagnosing cardiac pathologies. Eligible studies discussed ~~FDA~~ FDA-cleared, commercially available devices that were validated on an adult population. We summarize technical logistics of signal quality and device reliability, dimensional and functional features, and diagnostic value. In summary, our synthesis shows that reduced-set ECG wearables have huge potential for long-term monitoring, particularly if paired with real-time notification techniques. Such capabilities make them primarily useful for abnormal rhythm detection and there is sufficient evidence that a remote ECG device can be more superior to ~~a~~ traditional 12-lead ECG in diagnosing specific arrhythmias such as atrial fibrillation. However, this review identifies important challenges faced by this technology, highlighting the limited availability of clinical research examining their usefulness.

Keywords: ECG, electrocardiogram, diagnosis, remote, wearable, portable, atrial fibrillation

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~~1~~ 1 Introduction

The ~~Electrocardiograms~~ electrocardiogram (ECG) ~~are~~ is the most widely used diagnostic tool in clinical cardiology and is also one of the most widely collected body signals in wearable devices intended for diagnostic use. ~~The 12-lead ECG simultaneously acquires the electrical signal from several spatial directions enabling the assessment of the heart in a three-dimensional model.~~ ~~The ECG~~ The ECG is ~~is the most used diagnostic tool in cardiology and is~~ abnormal in a significant proportion of cardiac pathologies other than arrhythmias (coronary artery disease, heart failure, valvular heart disease, etc.), making it suitable for screening purposes ~~but in all these pathologies~~prior to subsequent evaluation by more specific ~~, other~~ diagnostic tests (echocardiography, ~~CAG~~coronary angiography, etc.) ~~are the ultimate diagnostic tools~~. The ~~12-lead~~ ECG is commonly acquired from 12 body surface leads ~~simultaneously acquires~~ to ~~the electrical signal from several spatial directions~~ enable~~ing~~ the spatial assessment of the heart in a three-dimensional model. However, ~~This makes it the "standard" diagnostic tool for most cardiac pathologies.~~ ~~T~~the 12-lead ECG is traditionally acquired by clinicians and trained personnel via a highly regulated procedure, limiting the scope of its clinical utility beyond the clinic. ~~However, i~~If one could trigger ECG recordings at the onset of worrisome cardiac symptoms, anytime and anywhere, clinicians would be provided with evidence of cardiac diseases that might no longer be apparent on the 12-lead ECG taken later at a medical appointment[1]. The latter objective has led to a widespread use of consumer-oriented remote and wearable ECG devices in recent years.

Information provided by the 12-lead ECG are interpreted following recommendations and expert-consensus statements. Fortunately, identifying basic arrythmias only requires one ECG lead[2], which drastically simplifies the task to the point of making possible its assignment to untrained individuals. Some solutions lie in the scope of wearables, which allow for a long-term ECG recording with an ergonomic design. There are also portable options, which do not provide continuous monitoring but allow a patient to quickly record one or multiple ECG leads in a range of non-clinical settings. These two types of devices–wearables and portables–make up the broader

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class of remote ECG devices.

~~A database search was conducted using PubMed to screen research articles with the following keywords 'wearable', 'portable', 'ECG' (or 'electrocardiogram') and 'diagnosis'. The targeted studies were the ones discussing commercially available, FDA cleared devices validated on an adult population. There was a restriction on study date to the last five years. Moreover, a manual search was carried out to identify commercially available remote ECG devices and link them to relevant research articles, forming a complete summary of the state-of-the-art products.~~

In this review article, we summarize the recent contributions, examine the reliability, and discuss the limitations of commercially available remote ECG devices in adult population. In doing so, we restrict our investigation to wireless products that claim a diagnostic value with a reduced set of electrodes. This paper ~~is primarily addressing~~also elaborates on ~~the following research questions: (1)~~ how ~~do~~ remote ECG devices overcome the disadvantages of the standard 12-lead ECG, ~~?~~as well as ~~and (3) what is~~ their clinical utility ~~of remote ECG devices~~ in diagnosing cardiac disease.~~?~~

~~1.1 Literature Search Strategy~~

~~This review was conducted in accordance with the adequate items of the Preferred Reporting Items for {Tricco, 2018 #124}Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines[3]{Tricco, 2018 #124}{Tricco, 2018 #124}{Tricco, 2018 {Tricco, 2018 #124}{Tricco, 2018 #124}{Tricco, 2018 #124}#124}. A database search was conducted using PubMed to screen research articles with the following keywords 'wearable', 'portable', 'ECG' (or 'electrocardiogram') and 'diagnosis'. The targeted studies were the ones discussing commercially available, FDA cleared devices~~

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~~validated on an adult population. There was a restriction on study date to the last five years. Moreover, a manual search was carried out to identify commercially available remote ECG devices and link them to relevant research articles, forming a complete summary of the state-of-the-art products.~~

~~2~~ 1 Basic 12-lead ECG function~~Review of Diagnostic statements made by a standard ECG~~

The 12-lead ECG can be used as a non-invasive assessment of a plethora of abnormalities, including arrhythmias and ectopic rhythm abnormalities, conduction defects and heart blocks, chamber hypertrophies and cardiomyopathies, inherited syndromes and channelopathies, myocardial ischemia and infarction, electrolyte abnormalities, medication toxicity, secondary cardiopulmonary manifestations, and other non-cardiac etiologies[3]. Thus, ~~Practice~~ practice guidelines by the American Heart Association / American College of Cardiology grouped the diagnostic statements for automated ECG interpretation in a list to promote uniformity of ECG diagnosis, yielding 117 potential diagnostic statements [4]. Figure 1 shows the ECG acquisition method and an example of the tracing and diagnostic statements available to clinicians.

~~The abnormal alterations identified on a 12-lead ECG could be associated to one of four categories of heart pathologies. First, rhythm disorders or arrhythmias, which constitute desynchrony in impulse propagation and interruption of the P-QRS-T sequence on the ECG. These arrhythmias can be supraventricular (occurring above the ventricles), including atrial fibrillation (AF), atrial flutter or paroxysmal supraventricular tachycardia; or ventricular (occurring in the ventricles), which comprise ventricular tachycardia and ventricular fibrillation. Identifying a~~

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~~basic arrythmia only requires one ECG lead because rhythm disturbance is present in all leads. The second category is conduction disorders. These abnormalities distort QRS signal morphology on the ECG. Many conduction defects require multi-lead criteria for diagnosis. The third category is chamber enlargement, which resembles a thickening of heart muscles. This results in altered voltage criteria and mean cardiac axis, and thus requires multi-lead ECG criteria for its diagnosis. Finally, myocardial ischemia happens in the case of lack of blood and oxygen supply to the heart muscles, which might lead to myocardial cell death (i.e., myocardial infarction). Cardiac ischemia leads to regional myocardial distortions that can be captured by ECG leads facing those myocardial regions, requiring multi-lead assessment for diagnosis.~~

The ECG signal needs to be filtered before analyzing it for diagnostic purposes. This is done by keeping a frequency band that preserves important prognostic physiological signatures needed for proper diagnostic statements. Guidelines specify the lower and upper filtering frequency bounds to guarantee an interpretable signal, respectively equal to 0.05 Hz and 150 Hz for adults[5]. Measuring abrupt events such as peak amplitude is more accurate when higher frequencies are kept in the signal after filtering[6].

~~3~~ Methods

~~1.1~~2 Literature Search Strategy

This review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines[7]. A database search was conducted using PubMed to screen research articles with the following search term: "(((wearable or portable) and (ECG or electrocardiogram)) and adult) and diagnosis) not PPG". The most recent search was performed on 3/1/2021 and was limited to the past 5 years. The search yielded 243 articles, which were subsequently filtered, first based on their title and abstract, then based on whether they were suitable for the study of the review's topic. The

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targeted studies were the ones discussing commercially available, FDA cleared devices validated on an adult population. Moreover, a manual search was carried out to identify commercially available remote ECG devices and link them to relevant research articles, forming a complete summary of the state-of-the-art products. Data extraction regarding study characteristics, device description and diagnostic utility metrics reported in that study was done by a single reviewer (ZB).

~~A database search was conducted using PubMed to screen research articles with the following keywords 'wearable', 'portable', 'ECG' (or 'electrocardiogram') and 'diagnosis'. The targeted studies were the ones discussing commercially available, FDA cleared devices validated on an adult population. There was a restriction on study date to the last five years. Moreover, a manual search was carried out to identify commercially available remote ECG devices and link them to relevant research articles, forming a complete summary of the state-of-the-art products.~~

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~~4~~ 2 SSummary of remote ECG devices with diagnostic capabilities

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~~4.1~~ 2.1 Commercialized ECG devices

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Table 1 shows the remote ECG devices that appeared most in the examined studies. Figure 2 specifies the placement of the electrodes used to obtain the ECG signal in each of these 8 remote ECG systems, while Figure 3 compares the features of standard 12-lead ECG to those of remote ECG devices.

~~4.2~~ 2.2 Real-time monitoring

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Most of the studied remote ECG devices have real-time monitoring capabilities. For example, intermittent portable ECGs recorded by AliveCor devices can be used as near real-time

systems thanks to wireless communication through a web-based portal. However, multiple ECG patches are non-real-time ECG monitors. In the case of the Zio Patch, a study has found that the median time to getting the clinicians to be aware of a significant symptomatic arrhythmia was equal to 19 days due to the time needed to return the device, analyze the ECG signals, create the report, and then notify the clinician[8]. However, most significant symptomatic arrhythmias were spotted on the patch within 7 days of the beginning of the monitoring, with all serious ones picked up within 4 days[8]. The patch has a great ability to capture significant arrhythmias in a timely way but there is a big gap between the time of detection and the time of diagnosis by the clinician. Real-time monitoring would address this problem.

A good representative of a real-time ECG patch system is the one implemented by the BioTel Heart MCOT Patch. Representative arrhythmia diagnostic strips are sent wirelessly to an independent diagnostic testing facility upon activation of threshold triggers based on the analysis of rate, rhythm irregularity, QRS morphology, and P-wave[9]. Notification criteria are set for a patient to alert the appointed physician and the patient[9]. In addition, clinical reports are made accessible to the health care provider during the monitoring period and when it is finished. The MCOT Patch had a significantly higher diagnostic yield than the auto-trigger looping event recorder for AF, bradycardia, ventricular pause, supraventricular tachycardia and ventricular tachycardia, as well as a significantly shorter mean time to diagnosis[9]. The MCOT patch thus pairs good diagnostic value with an efficient real-time use protocol and avoids the logistical problems associated with non-real-time monitoring devices.

~~5~~ 3 Remote devices signal quality

~~a.~~ 3.1 Factors that jeopardize signal quality

An ECG signal can be seriously compromised by noise, which might be a result of baseline wander and abrupt drift, power line interference, or muscle artifact[10]. ECG signals corrupted with noise are unreliable and must be filtered using noise-specific signal processing techniques before

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any manipulation or discarded in case recovery of a good-quality signal is impossible[10]. Ambulatory data recording from wearable devices is more likely to result in signals with artifacts than data obtained from bed-bound patients[11] because of the new challenges that daily-life movements introduce on the adherence of the electrodes and their placement. Also, external factors such as the contact with water while showering or swimming, or because of perspiration, may disrupt the recording system. Satija et al.[10] provides a review of ECG signal quality assessment methods to identify clinically acceptable single-lead and multi-lead ECG signals.

Remote ECG devices use alternative electrode positions (Figure 2) to record a specific number of leads. However, the electrode placement impacts the quality of an ECG tracing[12], and studies have demonstrated that a displacement as small as 20 mm might result in substantial modifications in ECG signal morphology[13]. Moreover, changes in the standard electrodes' positions affect the ECG tracings, where alterations along the left arm were the most visible compared to the right arm because of their relative distance to the myocardium, and a lateral site along the lower limb was more vulnerable to modifications in electrode placement relative to an anterior site[14].

~~b.~~ 3.2S Signal quality assessment

A few studies evaluated the signal quality of the obtained ambulatory ECGs. In particular, a group of publications, which investigated the feasibility of recording more than one lead using the Apple Watch Series 4, focused on this topic. The Apple Watch Series 4 was developed to record lead I. When lead II and lead III were self-recorded, the signals obtained were accurate and consistent with the standard ECG leads[15]. There was no clinical difference between the values of intervals, amplitudes and polarity computed for ECG segments in both standard and watch-based ECG leads I, II and III[16]. Setting the positive electrode situated at the back of the watch against the mid-abdomen showed good agreement of the watch-based ECGs with the corresponding standard ECGs. This method suggested the potential of the device to generate a 6-lead ECG by deriving the augmented limb leads aVL, aVF and aVR[17]. A brief research report kept the reference point on

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the leg to record leads II and III, but suggested recording bipolar chest leads as a substitute to the standard precordial leads (V1 to V6), impossible to trace in the need for an unavailable WCT "to connect the 3 limb electrodes", which were replaced by the right arm[18]. Consecutive recording of six-lead ECGs with the Apple Watch, representing Einthoven and Wilson-like leads, was possible with a good diagnostic signal quality and identical morphology as compared to standard 12-lead ECG[18, 19].

Further analysis to confirm those findings would qualify the Apple Watch to become a powerful tool that acquires a quasi-standard ECG anytime anywhere. Behzadi et al. highlighted the exceptional quality of the smartwatch ECG, free from significant baseline artifacts despite the absence of any skin preparation[16]. However, physical instability on the recording location (wrist or abdomen) could result in temporary artifacts[16].

The fidelity of the recorded signals was also reflected by the ability to obtain a reliable and accurate measurement of the QT interval from smartwatch recordings of lead I compared to the one from a standard ECG[20]. Similarly, a study using the 6-lead AliveCor KardiaMobile 6L ECG device compared its mean interval duration measurements (QTcF, heart rate, PR, and QRS) based on lead II against the standard ECG and concluded that this device is potentially useful in detecting clinically meaningful abnormalities[21]. However, it is important to be cautious when using measurements from a single ECG lead because waveform segmentation is ideally done using standard multi-lead criteria on 12 leads, for more stable and more accurate global measurements. Temporal superposition of complexes allows the detection of the earliest onset and latest offset of waveforms to compute more accurate intervals than those resulting from the segmentation of individual leads[5]. Single-lead ECG systems are prone to miscalculations, and any attempt to segment a lead, i.e., make measurements, is not equivalent to that operated on a standard ECG.

~~e.~~ 3.3 Implemented solutions to improve signal quality

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Commercialized remote ECG devices may compensate for the lost information due to the absence of a multi-lead recording by capturing the electrical activity in the heart from alternative

positions. In this framework, the BardyDx CAM, for instance, was developed to optimize P-wave quality. P wave clarity, morphology and its relationship with QRS are key factors to elucidate the mechanism of any arrhythmia[22], which might compensate for the absence of multiple views of the electrical activity in the heart. Moreover, the CAM patch is placed on the sternum which is located close to the atria with previous evidence pointing to the fact that “myocardial currents flow through the mediastinum to the skin overlying the sternum”[22-25]. Thus, the signal quality of the CAM patch was shown to be comparable to that of a Holter monitor based on reported high correlation coefficients between the two systems[22]. In another study, the signal clarity of the CAM patch was significantly improved compared to the Zio-XT patch as indicated by the physicians’ degree of certainty for deciding on a diagnosis[26].

4 Diagnostic value of remote ECG devices

~~6.1~~ 4.1 Diagnostic capabilities of remote ECG devices

Most clinical guidelines are based on 12-lead ECGs, which limits the diagnostic capabilities of reduced-set ECGs. Thus, most reduced-set ECG devices have primarily focused on abnormal rhythm detection, namely the detection of AF. This was recently highlighted by a collaborative statement on mHealth in arrhythmia management by leading societies in the field[27]. Figure ~~4xx~~ summarizes the diagnostic significance of remote ECG devices for AF detection. Yet, some other studies focused on the role of remote ECG devices for QTc interval monitoring or myocardial ischemia detection. A critical appraisal of this literature is provided herein.

A recent review by Witvliet et al.[28] emphasized the usefulness of handheld single-lead electrocardiograms in detecting AF. A previous systematic review and meta-analysis by Wong et al. evaluated the diagnostic accuracy of portable single-lead ECGs in comparison with a gold standard 12-lead ECG or Holter monitor, reporting high pooled sensitivities and specificities in community and in hospital settings[29]. Meanwhile, another systematic review and meta-analysis compared AF detection rate using portable ECG devices to Holter ECG monitoring, showing that studies that performed intermittent, multiple ECG recordings using portable devices for 19 minutes total produced equivalent AF detection rate to that of 24-hour Holter ECG recording[30].

Among the original research studies, Himmelreich et al. investigated the performance of an integrated algorithm for AF detection of AliveCor KardiaMobile compared to cardiologists' assessment of a simultaneously recorded standard 12-lead ECG showing that the AF detection algorithm had a high sensitivity and specificity[31]. These metrics slightly declined when evaluating the rhythm strips for any rhythm abnormality while a good diagnostic accuracy was maintained[31]. Specifically, less than 50% sensitivity was found when cardiologists tried to detect any conduction abnormality from the 1-lead ECG[31]. Another study showed the potential of this device to capture recurrent atrial fibrillation or flutter earlier in patients who underwent ablation or cardioversion and

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committed to daily intermittent monitoring, which was especially applicable for first month recurrence[32]. A multicenter randomized control trial has also shown that there is a significantly better identification of AF lasting 30 seconds or longer using a 30-day AliveCor KardiaMobile monitoring (with serial, intermittent 30-second ECG strips recorded 3 times a day) compared to a repeated 24-hour Holter monitoring, which represents the routine procedure used for patients who had a cerebral ischemic event but no known AF[33]. However, the authors noted that the device notifications indicating possible AF are mostly false positives with just a quarter of these detecting a true AF[33]. This finding highlights a low positive predictive value and, thus, a need to formally confirm the diagnosing before starting any treatment based solely on AF detection algorithms.

To further improve sensitivity, a 3-lead recording would reveal signatures of arrhythmias featuring a shift in electrical axis possibly invisible on single-lead signals. It would also better identify aberrant/broader QRS complexes when the leading edge of the QRS complex is relatively isoelectric to the only recorded lead (i.e., recorded lead is blind spotted); which is especially more applicable in the case of broad complex tachycardia[34]. ~~Before~~ Even after the release of the 6-lead AliveCor Kardia 6L[35], Frisch et al. slightly modified the ~~currently available~~ single-lead AliveCor KardiaMobile to extend its function to multiple-lead recordings[36]. The authors used~~ing~~ an alligator clip which enabled the device to record leads II and V1, in addition to lead I, for which the device is conceived[36]. It was demonstrated that the supplemental alternate leads significantly increased the accuracy of the ECG interpretation by cardiologists alongside their confidence in their decision[36].

The integration of ambulatory ECG devices in clinical practice to ensure AF monitoring would ameliorate resources utilization. Aljuaid et al. studied the impact of using the ECG Check device in a post-AF ablation population and found that the device was 100% sensitive and 97% specific for identifying atrial fibrillation or flutter after a 100-day follow-up period, with a notable, statistically significant decrease of AF-related outpatient department and emergency department visits[37].

~~Finally, r~~Remote ECG devices with reduced-set leads are not conceptually tailored toward

acute myocardial infarction detection. In particular, STEMI cannot be practically detected using a single-lead ECG since the diagnosis of STEMI requires the assessment of the ST-segment at the J-point in two contiguous leads as per the Fourth Universal Definition of Myocardial Infarction guidelines[38]. Lead I might show some changes with anterolateral infarcts or reciprocal changes with inferior infarcts, but it remains a poor screening tool, let alone, a diagnostic tool for STEMI. For instance, Avila ~~et al.~~ examined the potential role of a 3-lead ECG taken by the smartwatch in unveiling myocardial ischemia, where further specificity and sensitivity analysis are needed[17]. By adopting the multi-channel method to record not only leads I, II, and III, but also leads V1, V2, V3, V4, V5 and V6, the Apple Watch Series 4 could spot signatures of acute coronary syndrome visible on a 12-lead ECG, and specifically localize ST-segment alterations[39]. However, studies [36, 39] record Wilson-like leads which are conceptually not equivalent to precordial leads of a standard 12-lead ECG.

~~The surge of the COVID-19 virus impacted research in many ways.~~ Mobile Remote ECG devices have been shown to play a role in ~~s can help reduce patient-to-clinician contact while enabling acceptable QT or~~ QTc interval measurements for the purpose of ~~(remote)~~ patient's monitoring, especially during the current ~~The~~ surge of the COVID-19 ~~virus impacted research in many ways~~pandemic~~.~~ [21, 40, 41]. This was seen in a study using the AliveCor KardiaMobile 6L conducted in an inpatient setting during the COVID-19 era, in which stricter protocols for the monitoring of QTc intervals are required [42]. In this early preliminary work (n=4), it was found that remote ECG devices with 6 leads can be a reliable mean for accurate QTc measurements. Yet, these findings lacked ~~However, this work lacks a~~ larger scale assessment ~~of these findings~~, as well as a comparative study against ~~between the QT intervals measurements obtained by the 6-lead remote ECG and a~~ the 12-lead ECG as a gold standard ~~one~~ [42]. Thus, in a more recent study comparing remote 6-lead ECG to a standard 12-lead ECG in a larger cohort (n=182), authors found that ~~Also, another study has shown that the time of ECG registration has significantly diminished when adopting the same 6-lead device as compared to the 12-lead ECG, while~~ QTc

measurements did not differ between the two approaches, but the overall reliability of remote ECG was moderate (ICC = 0.56) ~~prolongation did not differ between three monitoring strategies COVID-19 patients were subject to (full monitoring using 12-lead ECG, 12-lead ECG at baseline and follow-up with KardiaMobile 6L, and full monitoring using KardiaMobile 6L)~~[43]. ~~Besides, no statistically significant difference was obtained for the mean QTc using the 12-lead ECG or, sequentially, the 6-lead device in a healthy control group~~ [43]. ~~At last~~Nevertheless, the authors noted the significantly lower time needed to obtain the remote-ECG compared to standard 12-lead ECG, suggesting a potential clinical utility for real-time QTc monitoring ~~moderate reliability of this technique and its feasibility~~ in ~~non-severely ill conscious~~ambulatory COVID-19 patients [43]. ~~Table 2 outlines the available published data examining the diagnostic utility of remote ECG devices discussed above.~~

~~6.2~~ 4.2 Advantages of longer monitoring periods and self-recorded ECG

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Long-term monitoring provides an increase in the diagnostic yield of heart monitoring methods for cardiac events such as AF[34, 44]. A comprehensive study on the duration of rhythm monitoring and the detection rate of AF, where the gold standard reference was an implanted loop recorder, showed that the 10-second ECG resulted in a sensitivity of 1.5% for AF detection[45]. This sensitivity increased to 8.3% for a 14-day monitoring period during which a 30-second ECG was recorded twice a day, and to 11%, 13%, 15%, 21%, and 34% for a single 24-hour, 48-hour, 72-hour, 7-day, or 30-day continuous monitoring, respectively[45].

Multiple studies tried to compare the signals recorded by Holter monitors, and other, remote ECG devices with continuous monitoring abilities. In fact, for long-term ECG analysis, Holter monitors are the gold standard to assign to patients suspected to have an underlying cardiac condition behind the preliminary findings of their medical assessment. The benefits of recording the ECG for a long period of time is to reveal the presence of transient cardiac events that might cause lethal heart problems if not detected timely. However, Holter monitors are cumbersome, and restrict the activities that can be performed while wearing them. Therefore, they

are commonly used for 24 or 48 hours, or less frequently, a week.

Smith et al. studied ECG signals simultaneously recorded on the patients with the BardyDx CAM patch and the standard Holter monitor over 24 hours[22]. Their work revealed a statistically significant higher performance of the CAM patch in identifying clinically pertinent events, including arrhythmias misdiagnosed by the Holter[22]. This was the only study we found that exclusively compared the diagnostic yield of an ambulatory ECG device to the Holter monitor over exactly 24 hours. Research on long-term ECG patches generally reports their performance over their optimal monitoring duration and compares the findings with the results of 24-hour Holter monitoring. In the case of the Zio Patch, a study opted for both approaches and reported the inability of the patch monitor to outperform the Holter over the 24-hour period, whereas the former identified significantly more events than the Holter monitor over a median wear time of 11.1 days[34]. Also, intermittent recordings using portable devices for a total of 19 minutes were as good as the 24-hour Holter ECG recording in detecting AF[30].

4.3 Lack of studies on clinical utility

We found a limited number of research articles examining the clinical utility of remote ECG devices. Besides, the median sample size for the reviewed studies is 102~~.~~5 subjects (IQR = 50-2142~~0~~). Hence, the reviewed studies were likely underpowered to detect significant clinical differences, given that the rate of the cardiovascular diseases defined as outcome is low. Only one study was looking at a large-scale sample (n=78,490 subjects)[9]. More studies should investigate the performance of remote ECG devices on larger numbers of participants. Conducting power analyses before data collection would provide a solid ground to draw statistically significant conclusions. A further problem is that, while studies acquired remote and standard ECG (or Holter monitor) recordings simultaneously[22, 31, 34, 39], other studies accomplished this task in a sequential fashion[43]. This lack of rigor might jeopardize the findings of the study by a loss of fairness during

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the comparison of the outputs of the two systems. Also, there were other articles that presented different findings. For instance, as the Apple Watch Series 4 reads the ECG rhythm strip as sinus rhythm, AF or inconclusive, it was shown that multiple AF events were missed by the algorithm where it only provided notifications with a 41% sensitivity for AF and reported 31% of the ECGs to be inconclusive[46].

5 Challenges and limitations of remote ECG devices

~~7.3~~ 5.1 Signal filtering bandwidth

Recording higher frequency signal consumes more battery and memory, which is problematic for remote ECG systems. Guidelines relax the upper frequency to 60 Hz in ambulatory devices. Such frequency can suppress the excessive noise and interferences introduced by daily activities, excessive movement, perspiration, electrodes' adhesion, and electrodes' detachment. The downside is that a frequency as low as 40 Hz affects the QRS complex and nullify amplitude measurements, impacting the performance of R peak detection used in almost all ECG signal processing algorithms and, hence, potentially leading to imprecise diagnostic decisions, especially in conditions such as AF[47]. There is no analysis of the impact of signal filtering on the quality of the ECG signal obtained from remote devices and its ability to derive diagnostic statements. For example, the ECG Check from Cardiac Designs has a very narrow bandwidth from 0.5 Hz to 25 Hz, which explains the limited statements that it can make ("Normal", "Irregular HR", "Unable to read ECG"). On the other hand, AliveCor KardiaMobile and BioTel Heart MCOT patch have sampling rates equal to 300 and 250 samples per second (Hz), respectively, which would allow an upper bound of the processing filter bandwidth to be at most equal to 150 Hz and 125 Hz, respectively, based on the ~~he~~ Nyquist-Shannon sampling theorem to prevent aliasing. Precise data about such technical aspect are very important in assessing the utility of the recorded signal, yet they are hard to find in published studies.

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5.2 Real-time need

As mentioned in section 4.3, the high potential of remote ECG devices is hindered by both the absence of real-time interaction with the healthcare professionals and the lack of a prompt notification of the user in case of detection of possible abnormalities. The first week of monitoring using the Zio patch revealed most significant symptomatic arrhythmias[8], but the report was only available after 14 days. This issue is extended to many remote ECG devices, where the lack of a timely alarm constitutes a missed opportunity to provide timely diagnosis and treatment.

5.3 Device acceptability

~~a.~~ User acceptability and compliance

a.

The main factors to investigate in the assessment of the user acceptability of the device depend on the nature of the device. Handheld devices and smartwatches are simple to manipulate as opposed to patch devices, for which it is challenging to identify the correct location; a solution for better compliance would be including a patch placement template in the kit as done for BioTel Heart MCOT Patch. However, it is worth noting that the use of portable ECG devices might be difficult for older adults. In the case of the AliveCor KardiaMobile 6L, for instance, the application of the device to the left knee or ankle might be challenging for elderly patients and the data acquisition might be hindered due to their clinical status which could result in a lack of collaboration from the subjects[43].

Additionally, skin irritation is a big challenge to user acceptability and compliance in the case of wearable ECG patches, which are intended for an extended monitoring period. The BardyDx CAM, for instance, was found to be gentler on the skin with no severe skin irritation reported over 24-hour use compared to 3 cases of severe reactions in Holter patients, representing 6% of the studied sample[22]. Since the CAM patch interfered significantly less with daily activities and sleep, and has better adherence, the surveyed patients preferred it to the

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Holter monitor, and the technicians noted that it is easier to attach to patients[22].

b. Acceptability among healthcare professionals

~~a.~~

A survey of current perspectives on consumer-available digital health devices for detecting atrial fibrillation among cardiac healthcare practitioners revealed that most of them have recommended a digital device for AF detection[48]. While 42.7% of the respondents indicated that the 30-second single-lead ECG was enough to recommend oral anticoagulation for patients at high risk for stroke, a majority required further investigation of the performance of digital devices relative to conventional AF monitoring devices, and 53.4% demanded their professional societies issue guidelines to ensure their optimal use[48]. Pitman et al. found that relying solely on the automated algorithm of the AliveCor KardiaMobile to screen for AF does not reach the desired performance, but the latter can become very good if the algorithm's output is supplemented by clinical judgement and recordings are repeated in case of an insufficient quality[49]. Regarding the use of portable single-lead ECGs by cardiologists in particular, Himmelreich et al. showed that cardiologists can accurately diagnose AF from a single-lead ECG with high sensitivity and specificity for detecting any rhythm abnormality, and a less than 50% sensitivity and a perfect specificity for detecting any conduction abnormality[31]. These results demonstrate single-lead ECG device is well accepted by cardiologists for detecting rhythm abnormalities, but less suitable for identifying conduction abnormalities, which might raise patient safety concerns in the context of false negatives. On the other hand, a study investigated general practitioners' skills in interpreting handheld single-lead ECG and showed that they are competent in excluding cardiac arrhythmias without risk[50]. However, the low positive predictive value of general practitioners for the identification of AF or flutter as compared to consensus by a panel of cardiologists suggests the pressing need for cardiologist's over-reading of remote ECG tracings[50]. It was found in the same study that providing the outcome of the automatic AF-detection algorithm didn't ameliorate the interpretation skills of the general practitioners[50].

A main challenge of the increasing use of remote ECG devices is their burden on

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healthcare professionals as a potential consequence of the enormous increase in false positive referrals. For example, it has been shown that a diagnosis of AF could be confirmed by cardiologists in only 34% of cases identified by Apple Watch and up to 65% of cases identified by Kardia Mobile[51]. Thus, automated diagnosis of AF using mobile devices remains an approximation of the current reference standard. Nevertheless, the demonstrated benefits of mobile devices for early detection of AF in those with unknown history and in need of oral anti-coagulation is undeniable. Chan et~~.~~ al. report that the number needed to screen for a new AF diagnosis in adults older than 50 years of age is 145 at device detection rate of 2.6% and positive predictive value of 65%[52]. To interpret these numbers, if a cardiologist prescribes a device for 145 patients, a mobile device will identify roughly 3 patients with possible AF. Among those three: one would be a false positive referral; one would be a known history of AF; and one would be a newly diagnosed AF case. Yet, continuous refinement of current automated ECG interpretation algorithms, including the adoption of artificial intelligence (AI)-enabled classification algorithms, can play a significant role in improving the specificity of device-provided AF diagnosis and, hence, in reducing the absolute number of false positive referrals in the upcoming decade[53].

Finally, ~~Little~~ little has been done about the integration of remote ECG devices with existing electronic health record (EHR) systems, which brings additional challenges, including the burden of a large amount of information on physicians[54]. For example, physicians might have to deal with too many false positive referrals, forcing them to look over great quantities of ultimately unimportant information.

~~7.4~~ 5.4 Privacy, security and safety

Wearable biomedical devices inherently deal with confidential health information unavailable for public access by healthcare entities, which employ strict methods to enforce related regulations. This raises multiple issues especially with the poor integration of this data with EHR. Izmailova et al.[55] provides methodological and logistical considerations for the implementation of wearable technologies in clinical trials, presenting data security as one of the

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challenges to the deployment of these devices. General issues also include guaranteeing secure data collection, storage, transmission and receipt, secure account management, and data encryption and blinding[55]. The practicality and diagnosis automation of the novel portable ECG devices come at the expense of an increased manipulation of health information, raising questions about the reliability of the storage medium and the access protocol.

One approach to address this problem may be by taking decisions at the hardware level. One can design a “physically secure communication” by opting for human body communication which constrains the signals to be in the body[56]. The large-scale Apple Heart Study examined measures taken to prevent any violation of data security and privacy regulations, such as Title 21 Part 11 of the Code of Federal Regulations, and made private health information inaccessible to Apple, the sponsor of the study and the manufacturer of the phone, the watch and the algorithm[57].

~~7.57.3 Lack of studies on clinical utility~~

~~We found a limited number of research articles examining the clinical utility of remote ECG devices. Besides, the median sample size for the reviewed studies is 102.5 subjects (IQR = 50-220). Hence, the reviewed studies were likely underpowered to detect significant clinical differences, given that the rate of the cardiovascular diseases defined as outcome is low. Only one study was looking at a large-scale sample (78490 subjects)[9]. More studies should investigate the performance of remote ECG devices on larger numbers of participants. Conducting power analyses before data collection would provide a solid ground to draw statistically significant conclusions. A further problem is that, while studies acquired remote and standard ECG (or Holter monitor) recordings simultaneously[22, 31, 34, 39], other studies accomplished this task in a sequential fashion. This lack of rigor might jeopardize the findings of the study by a loss of fairness during the comparison of the outputs of the two systems. Also, there were other articles that presented different findings. For instance, as the Apple Watch Series 4 reads the ECG rhythm strip as sinus rhythm, AF or inconclusive, it was shown that multiple AF events were missed by the algorithm.~~

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~~where it only provided notifications with a 41% sensitivity for AF and reported 31% of the ECGs to be inconclusive[46].~~

~~6~~ 6 Conclusion

Remote ECG devices ~~have~~ provide incremental benefits ~~in comparison to~~ over the ~~gold~~ standard 12-lead ECG or ambulatory Holter monitors in multiple aspects. They can facilitate the accurate and timely diagnosis of heart rhythm abnormalities, namely AF. The potential integration of these tools in clinical settings or at home conditions give an unprecedented flexibility for patients to self-monitor their heart health without interrupting daily activities or scheduling doctor visits. They also improve diagnostic value by allowing for long-term monitoring, particularly if paired with real-time notification techniques. Multiple aspects and applications of the devices, such as ~~factors~~ compliance issues ~~to their~~for consistent use, are still to be investigated but their current use is promising [58].

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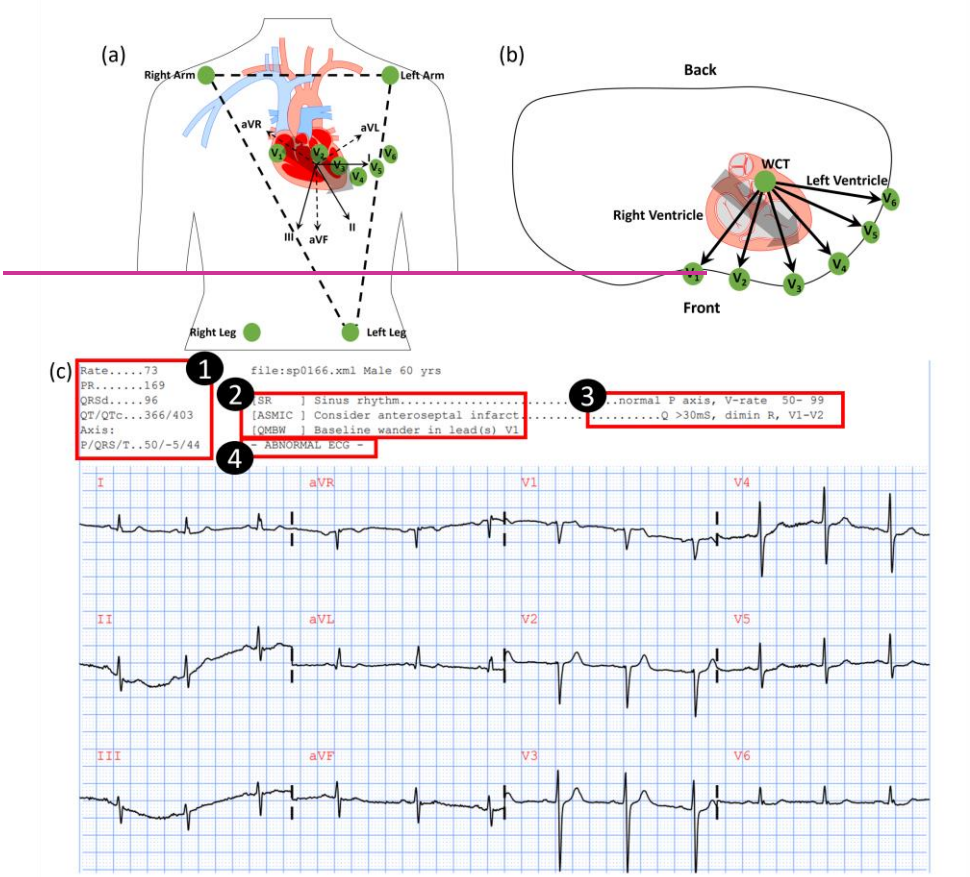
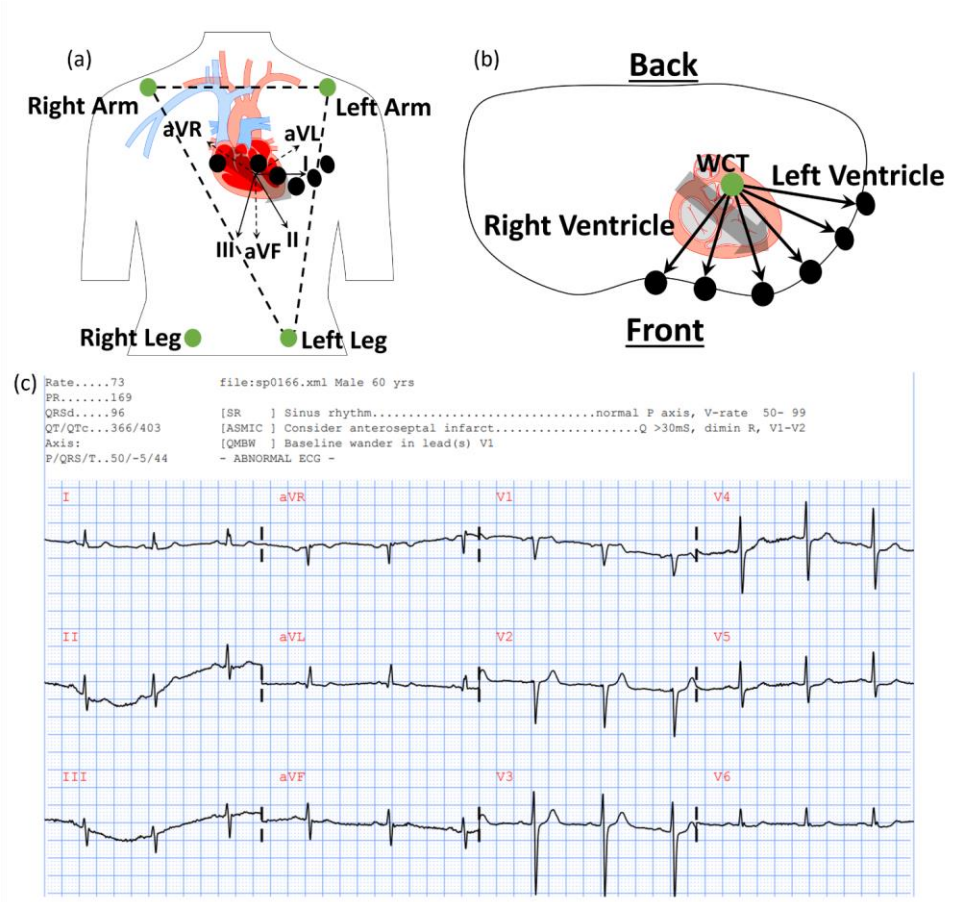
Figures:

Fig. 1: ECG acquisition method and tracing.





(a) Frontal ECG leads and (b) Precordial ECG leads acquisition methods.~~:~~ The black dots represent the electrodes; (c) An example of a standard 10-second 12-lead ECG ~~with acute coronary occlusion~~from a 60-year-old male evaluated for acute chest pain. ~~, where t~~The header of the ECG page ~~s~~shows~~ing~~ global measurements of the ECG waveforms (left) ~~(#1),~~ diagnostic statements made by the machine and an overall automated interpretation (center) ~~(#2),~~ and the corresponding decision criteria (right). ~~(#3), and the overall automated interpretation (#4).~~ WCT: Wilson's central terminal for calculating the ECG signal for the unipolar precordial leads.

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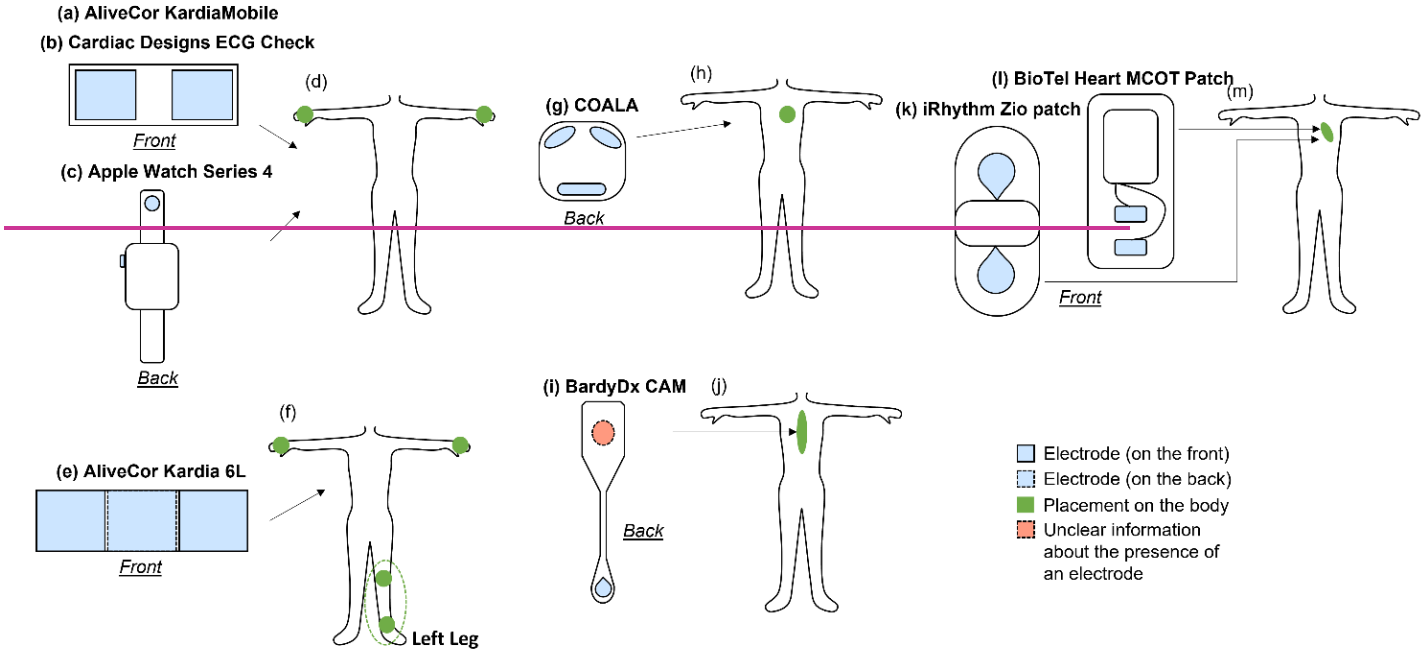
Reviewer 1: Figure 1: this ECG does not meet the universal definition of myocardial infarction criteria ST-segment elevation myocardial infarction

Fig. 2: Commercialized remote ECG devices and their placement.



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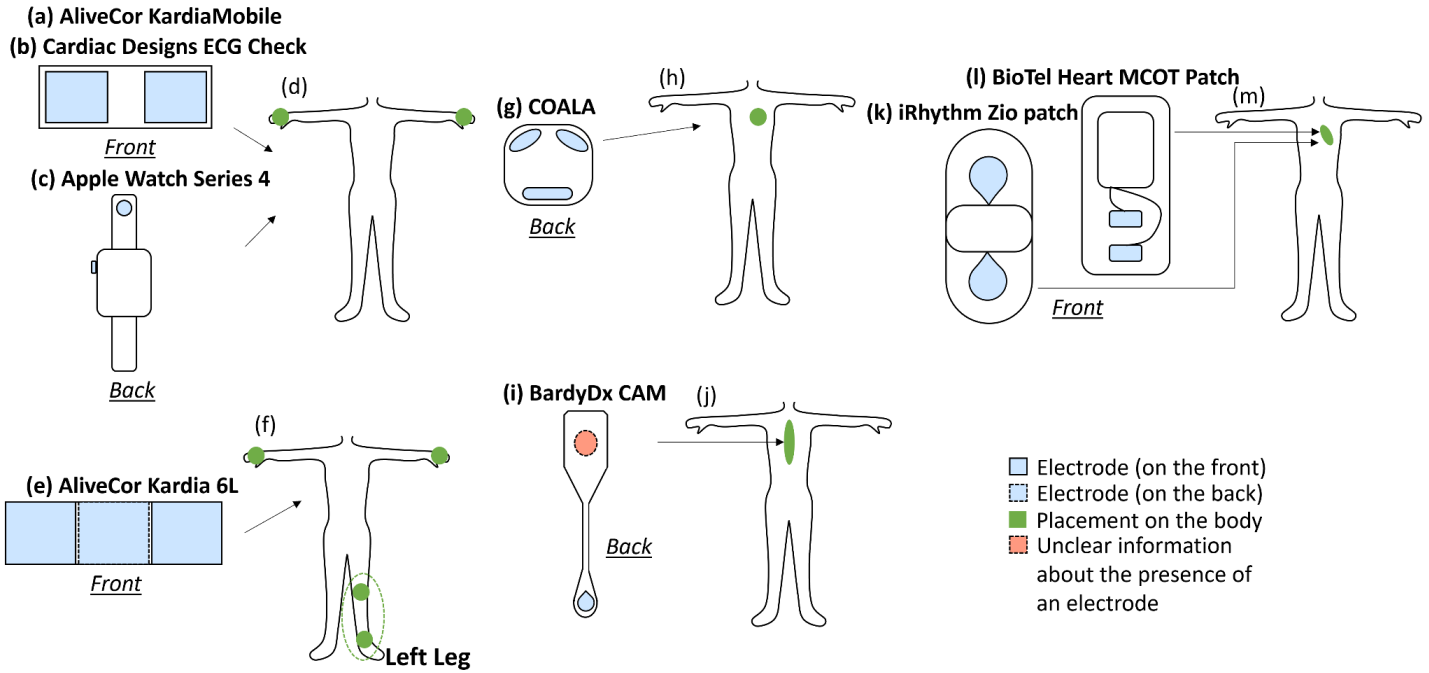
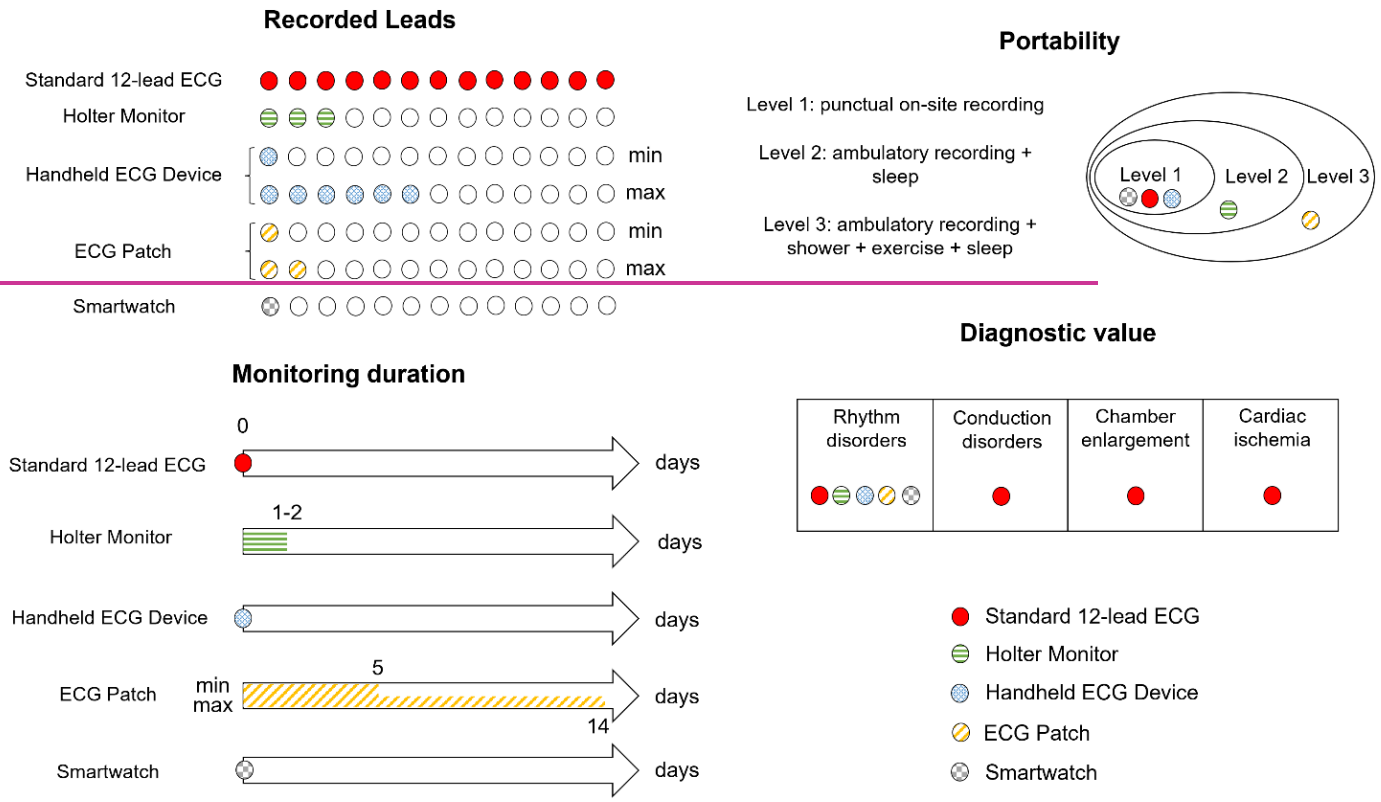


(d) the placement of the two sensors of (a), (b) and (c); (f) the placement of the three sensors of (e); (h) the placement of the three sensors of (g); (j) the placement of the sensors of (i); and (m) the placement of the sensors of (l) and (k) to record the ECG signal.

Fig. 3: Comparison of the features of standard vs. remote ECG monitoring systems.



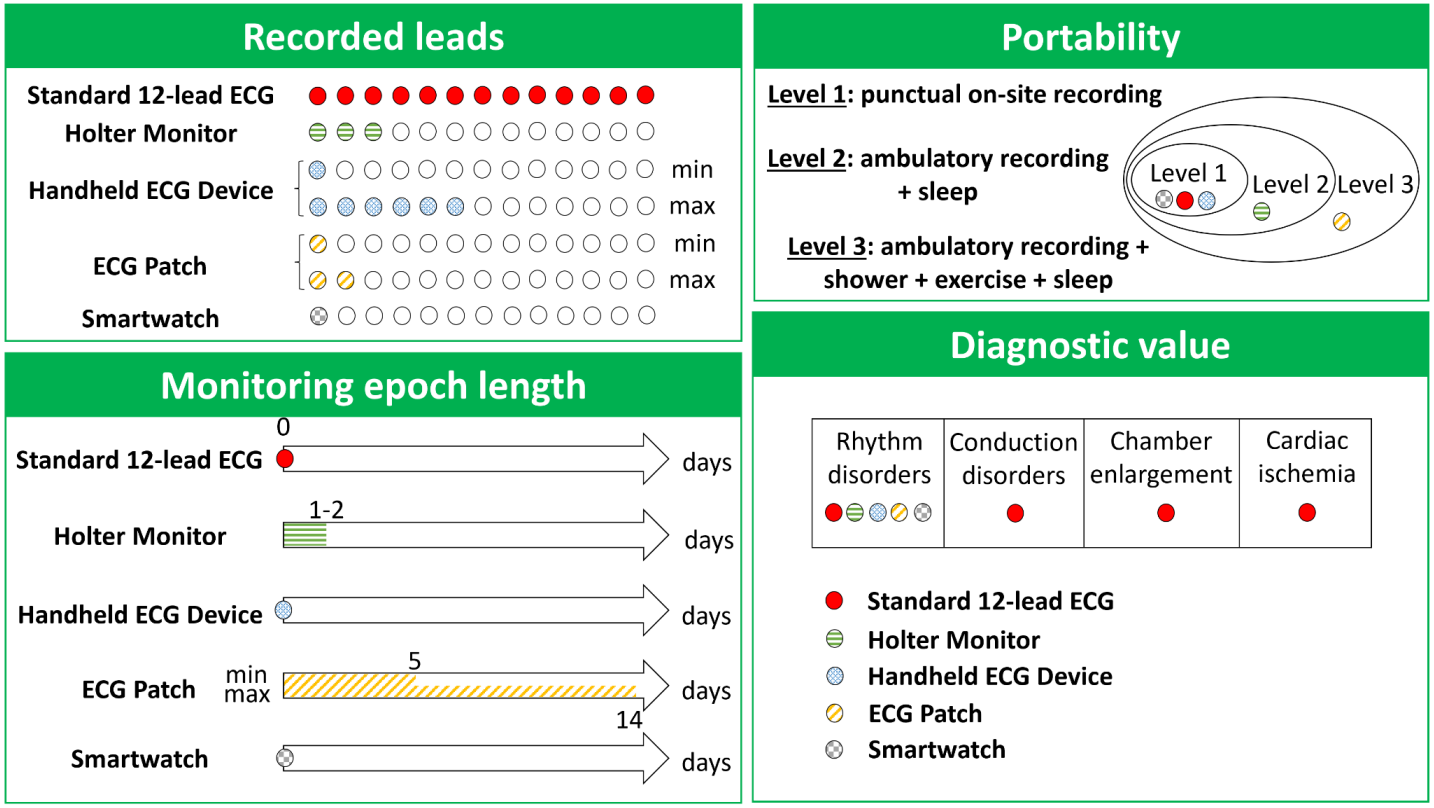
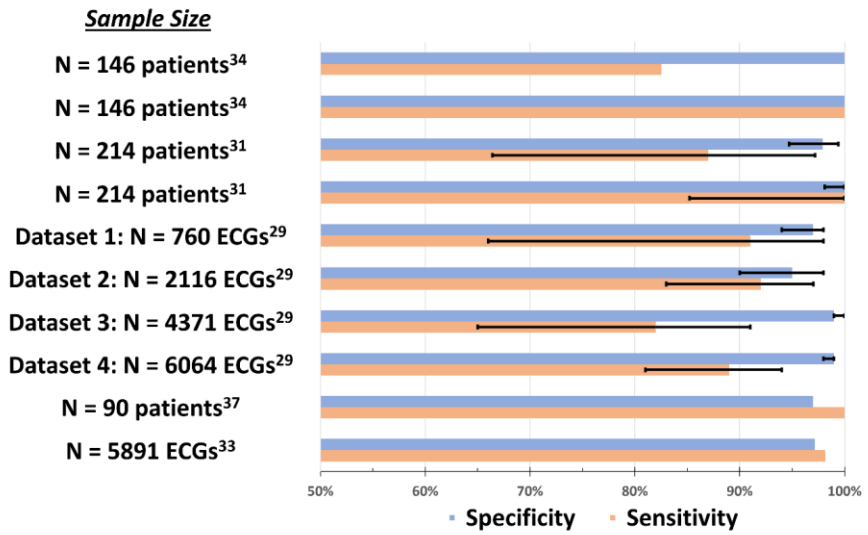

Recorded leads
Standard 12-lead ECG
Holter Monitor
Handheld ECG Device
min
max
ECG Patch
min
max
Smartwatch
Portability
Level 1: punctual on-site recording
Level 2: ambulatory recording + sleep
Level 3: ambulatory recording + shower + exercise + sleep
Level 1
Level 2
Level 3
Monitoring epoch length
0
Standard 12-lead ECG
days
1-2
Holter Monitor
days
Handheld ECG Device
days
5
ECG Patch
min
max
days
14
Smartwatch
days
Diagnostic value
Rhythm disorders
Conduction disorders
Chamber enlargement
Cardiac ischemia
Standard 12-lead ECG
Holter Monitor
Handheld ECG Device
ECG Patch
Smartwatch

Fig. 4: ~~An outline of~~ Summary of the diagnostic ~~significance~~accuracy of remote ECG devices for AF detection.



This figure summarizes the reported sensitivity and specificity metrics for detecting AF using a wearable device. Error bars indicate the 95% confidence interval as reported by parent study. Metrics without error bars indicate parent study did not report such values or the independent reviewer computed these metrics from data extracted from the parent study. [29, 31, 33, 34]

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Table 1: Examples of Remote ECG Devices

Remote ECG Device	Number Of ECG Leads	Continuous Monitoring Duration	Real-time	Require prescription?	Data storage and manipulation	Diagnostic claims
Handheld device						
AliveCor KardiaMobile	1 lead	NA	Yes	No	Stores data on the phone or emails it to doctor	Detects Atrial Fibrillation, Bradycardia, Tachycardia, Sinus Rhythm with SVE, Sinus Rhythm with Wide QRS, and Sinus Rhythm with PVCs
AliveCor Kardia 6L	1 lead/6 leads	NA	Yes	No	Provides secured cloud storage and cardiologist reviews	
Cardiac Designs ECG Check	1 lead	NA	Yes	No	Stores and transmits the ECG data to a medical professional via a secure cloud server or email for users with a prescription	Displays normal, Irregular HR, Unable to read
COALA	2 leads	NA	Yes, with on demand ECG reports	Yes	Recordings are easy to access with automatic interpretation and real-time r ports in the cloud based COALA Care portal	Diagnoses symptomatic arrhythmias (9 of the most common arrhythmias) or murmurs, P-wave based AF detection
Patch						
BardyDx CAM	1 lead	14 days	No	-	Upload data to the Cloud through a secure web-based portal	P-wave centric sternal ECG monitoring
BioTel Heart MCOT Patch	2 leads	5 days	Yes	Yes	Data transferred to trained technicians and look for specific heart activity 24/7 and may contact your health care professional,	Assists in diagnosing certain heart arrhythmias

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					clinical reports are available to your clinician during and at the end of your service	
iRhythm Zio patch	1 lead	up to 14 days	No	Yes	-	Generates main findings in a report
Smartwatch						
Apple Watch Series 4	1 lead	NA	Yes	No	Saves the results (ECG and analysis) in the Health app of the iPhone and can be shared as a PDF with the doctor	Classifies the recording as sinus rhythm, bradycardia, tachycardia, or atrial fibrillation or as inconclusive

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