Clinical update

Mobile technology and the digitization of healthcare

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The convergence of science and technology in our dynamic digital era has resulted in the development of innovative digital health devices that allow easy and accurate characterization in health and disease. Technological advancements and the miniaturization of diagnostic instruments to modern smartphone-connected and mobile health (mHealth) devices such as the iECG, handheld ultrasound, and lab-on-a-chip technologies have led to increasing enthusiasm for patient care with promises to decrease healthcare costs and to improve outcomes. This 'hype' for mHealth has recently intersected with the 'real world' and is providing important insights into how patients and practitioners are utilizing digital health technologies. It is also raising important questions regarding the evidence supporting widespread device use. In this state-of-the-art review, we assess the current literature of mHealth and aim to provide a framework for the advances in mHealth by understanding the various device, patient, and clinical factors as they relate to digital health from device designs and patient engagement, to clinical workflow and device regulation. We also outline new strategies for generation and analysis of mHealth data at the individual and population-based levels.

Keywords   Digital health • mHealth • Medical technology • Sensors • Patient-generated data

The digitization of healthcare

Within these early years of the 21st century, we have witnessed remarkable technological progress with the developments of powerful and portable computing devices. Simultaneously, a global connection resulting from broadband and satellite technologies has resulted in an increasing number of 'connected users' for information sharing. The emergence of new mobile health (mHealth) technologies has resulted from the temporal intersection of several coincidental movements: (i) an urgent need to address the rising burden of chronic diseases; (ii) Moore's law—the exponential increase in computing power resulting in the development of smaller and cheaper mobile electronics[1]; and (iii) shifting healthcare model to an increasingly patient-centric designs.[2] mHealth is defined by the practice of medicine supported by portable diagnostic devices. Use of these devices at the point-of-care is resulting in a change in the method of healthcare delivery from one that was health-systems generated to one that is remote and patient generated.[3,4] The culmination of these factors presents unparalleled opportunities to increase patient engagement, to reduce healthcare costs, and to improve outcomes.[5]

To reach the transformative potential of mHealth, a great deal of validation of the technical capabilities and accuracy, as well as the clinical impact of these technologies, is needed before we know they are effective. The real-world practice of medicine is complex and raises important questions on how we can generate clinically meaningful digital health data. Clinicians are beginning to enquire whether more devices necessarily mean more information and if some information may be redundant or even unnecessary. As mHealth devices become increasingly available, three important questions arise: who should be the first digital health adopter: the patient, the provider, or the healthcare system? What factors of mHealth are most effective? And what is the evidence supporting the clinical utilization of such devices? As we aim to determine the effectiveness of these technologies, what are the outcomes—morbidity and mortality—or are patient-generated outcomes such as quality of life equally important? Are patients prepared to understand mHealth findings particularly elderly patients or those with complex disease states? Do patients modify their behaviour? Will user-generated data lead to patients seeking out therapies for digital data rather than true disease states? We present these questions as they relate across the digital device, the digital patient,

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and the digital clinic (*Figure 1*), and discuss the literature evaluating mHealth towards their answers.

Digital devices

Which components of digital devices make them usable and how do these devices help to solve clinical problems? Five classifications of mHealth technologies have been developed: smartphone health 'apps' (>160 000 currently available),[6] smartphone-connected devices; wearable and wireless devices; handheld-imaging platforms, and miniaturized sensor-based technologies.[7,8] Conditions such as hypertension, diabetes, and heart failure (HF), as well as medication adherence monitoring, have seen significant advances across most technological categories (see Supplementary material online, *Table S1*). As new technologies are devloped, data transfer becomes increasingly important, especially when considering how data derived from mHealth devices integrates into clinical workflows. In general, a closed data loop is necessary and involves a cycle initiated by the patient or provider, followed by Internet (cloud)-based data transfer, interpretation of these findings or automated algorithms, and the data being returned to the patient and provider for clinical decisions (*Figure 2*). Herein, we discuss several mHealth technologies that have been approved for use by EU and US regulatory authorities and how such technologies advance our understanding of common clinical problems.
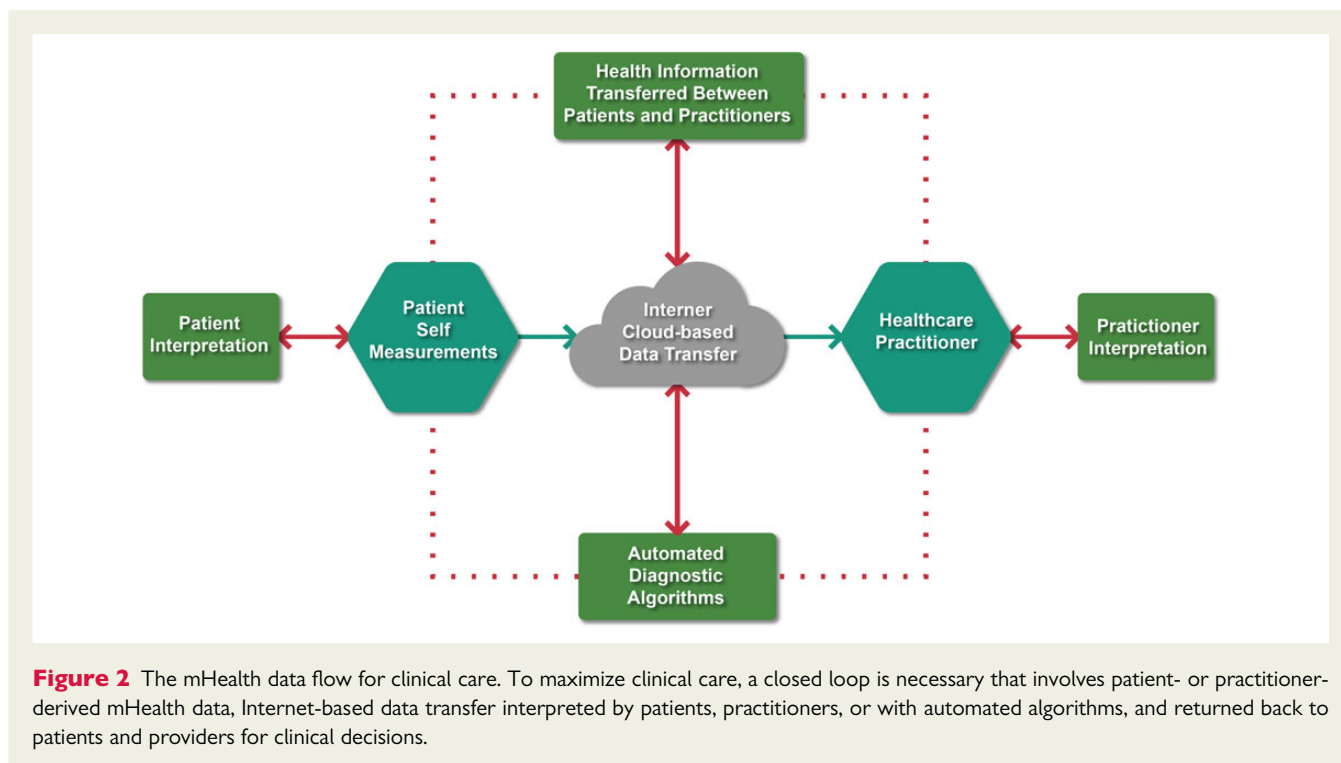
Smartphone-connected rhythm monitoring devices

One such technology is the iECG, a smartphone case that incorporates electrodes for wireless cardiac telemetry monitoring (AliveCor), and was approved for use by the US Food and Drug Administration (US-FDA) and EU Medical Device Directive (EU-MDD) in 2013. A 30-s single-lead (lead I) rhythm strip is produced by a case-like attachment when held in the right and left hands. A real-time display of the cardiac rhythm is created by conversion of an electrical signal into ultrasound and is captured by the smartphone microphone. Automated algorithms were developed and approved for use, which provide the user with an immediate rhythm analysis of atrial fibrillation (http://www.accessdata.fda.gov/cdrh_docs/pdf14/K142743.pdf). To maximize the clinical effectiveness, the iECG should be used among patients at high risk for the development of an arrhythmia, and to capture the arrhythmia in real time for prompt clinical decisions. For example, the occurrence of sub-clinical atrial arrhythmias is a well-known cause of a cryptogenic stroke.[9] Compared with usual care and intermittent monitoring strategies, studies investigating extended 6-month electrocardiographic monitoring with external event monitoring devices or internal devices such as pacemakers and loop recorders have identified a 9−16% incidence of sub-clinical atrial fibrillation among patients with known cerebrovascular disease and among those with hypertension, diabetes, or ischaemic heart disease.[10−12] In the aggregate, ∼10 such patients need to be screened with extended monitoring to establish one new diagnosis of atrial fibrillation.[9] The iECG is not designed as a continuous rhythm monitor; however, the relatively low cost (US$70−90 or £70−90) and high patient utilization make it a potentially practical alternative to monitor high-risk individuals for a prolonged duration.[13] Several potential clinical applications of the iECG have recently emerged.
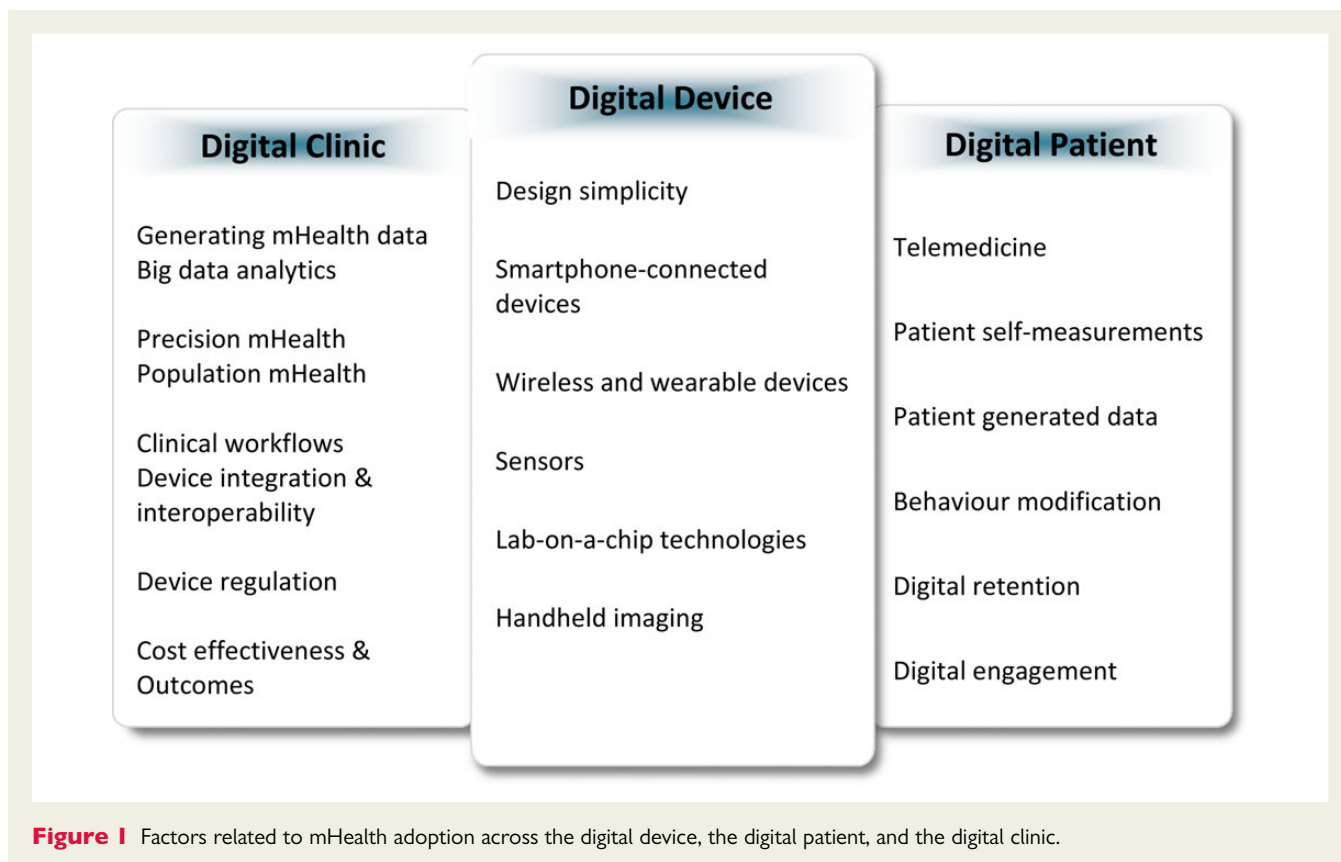
Figure 1 Factors related to mHealth adoption across the digital device, the digital patient, and the digital clinic.

Figure 2 The mHealth data flow for clinical care. To maximize clinical care, a closed loop is necessary that involves patient- or practitioner-derived mHealth data, Internet-based data transfer interpreted by patients, practitioners, or with automated algorithms, and returned back to patients and providers for clinical decisions.

The iTRANSMIT investigators demonstrated a 100% diagnostic accuracy of the iECG to detect the recurrence of an atrial arrhythmia after an ablation when compared with traditional transtelephonic monitoring.[14] Future developments include extending the single-lead monitor to multiple iECG leads for remote monitoring of an acute coronary syndrome.[15]

Wireless and wearable devices

Analogous to smartphone-based devices, continuous blood pressure and glucose-monitoring technologies have also been developed. In contrast to intermittent cuff-based blood pressure devices, continuous 24-h ambulatory devices have been manufactured and form fitted to watch-like configurations (BPro, HealthStats Inc.). Approved for use in 2014, the device uses applanation tonometry by applying mild pressure to partially flatten the radial artery to acquire measurements of central aortic systolic pressure. The subsequent systolic waveform produces a digital blood pressure signal from the radial artery to the overlying watch that is transmitted at 15-min intervals and recorded for up to 24 h (Supplementary material online, *Figure S3A*). The findings from Ambulatory Central Aortic Pressure study demonstrated the application of this technique and compared the watch-like device with conventional cuff-based ambulatory measurements.[16] Among 171 hypertensive participants, tonometric measurements correlated within a 5-mmHg margin to conventional ambulatory measurements and tracked the reduction in blood pressure with antihypertensive therapy over a follow-up duration of 3 months. Continuous monitoring of blood pressure in the ambulatory setting may be important among patients with drug resistant hypertension or those with orthostatic hypotension. Continuous glucose monitoring

(CGM) with minimally invasive sensor technologies (Dexcom) involves the implantation of a small transcutaneous electrode into the subcutaneous tissue of the abdomen or arm where a glucose oxidase chemical reaction produces a current reflecting the interstitial glucose concentration.[17,18] This electrical signal is converted into glucose concentrations and is transmitted to a smartphone or tablet computer at 5-min intervals for real-time continuous monitoring (Supplementary material online, *Figure S3B*). Several aspects of CGM are proving effective among diabetic patients including the prevention of hypoglycaemic episodes with early detection, and as a method for long-term glycaemic control resulting from positive behavioural changes such as diet, exercise, and medication compliance that are facilitated by the awareness of glucose measurements and real-time trends.[19]

Implantable and ingestible sensors

Unlike the average car that is equipped with sensors that gauge the vehicle's position, speed, and fluid levels alerting the driver when readings are out of range, the human body has not been designed with similar alert mechanisms to monitor internal physiological functions. Nanoparticle biosensors have been designed with some that are fully implantable. These sensors act as a 'fuel gauge' transmitting internal measurements of physiological function in a step towards digitizing the human body.[20,21]

Implantable sensors

The signs and symptoms of congestion in HF commonly precede changes in vital signs or those markers that predict a decompensation. Presently, the assessment of filling pressures in the ambulatory setting include devices that measure right ventricular and pulmonary

artery pressures.[22] Approved in 2014, the CardioMEMS device is a fully implantable micro-electromechanical pulmonary artery pressure monitoring system (Supplementary material online, *Figure S3C*). The sensing platform is designed with a combination of an inductor coil and a pressure-sensitive capacitor creating a resonant circuit that changes in response to pressures. The system is leadless and battery-free, and is implanted with passive fixation during a right heart catheterization. Pulmonary artery pressure is continuously monitored, and sensor readings are wirelessly transmitted to an external unit and to a cloud-based platform for clinical review. The CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial was a prospective, single-blind study that randomized 550 class III patients with a prior HF hospitalization to the Cardio-MEMS device with wireless implantable haemodynamic monitoring (W-IHM), or to controls with an implanted device and monitoring turned off.[23] Patients were instructed to take daily measurements, and a review of pressure data by trial coordinators occurred at least once weekly. At 6 months, W-IHM was associated with a 30% reduction in HF readmissions (hazard ratio 0.70, 95% CI 0.60−0.84, $P < 0.0001$), a shorter HF-related hospital length of stay among those admitted for treatment (2.2 vs. 3.8 days, $P = 0.02$), and was associated with a greater number of changes to neurohormonal and diuretic therapies than was the control group (nine changes per patient vs. four, $P < 0.0001$). A *post hoc* analysis among 119 patients with HF and preserved ejection fraction showed that the 6- and 18-month HF readmission rates were 46 and 50% lower in the W-IHM group than in controls, respectively.[24] These results underscore the significance of remotely monitoring cardiopulmonary pressures, and may be of particular significance in the preserved ejection fraction cohort given the lack of effective therapies to mitigate adverse outcomes in this population.

Ingestible sensors

Non-adherence to medications has been documented to occur in >60% of patients with cardiovascular diseases and remains one of the most common contributing factors resulting in symptoms recurrence and adverse outcomes.[25] Wireless observed therapy with a novel ingestible sensor (Proteus Digital) is an approved and unique technology to monitor medication compliance.[26] This system consists of two major components: an edible sensor and a wearable receiver patch. The edible sensor is an integrated circuit with 1 mm in diameter and 200 μm in thickness, and is composed of magnesium and copper (Supplementary material online, *Figure S3D*). Gastric fluids activate the sensor, and an electrochemical reaction produces a voltage across the circuit creating a biogalvanic battery and an electrical field. The signal remains active for 8−10 min and is transmitted to an overlying Band-Aid size abdominal patch. The digital data are subsequently transferred to a smartphone application and a cloud-based platform for review by patients and practitioners. The safety and performance of this networked sensor system has been evaluated in patients with hypertension and HF, and has demonstrated a positive detection accuracy of 97% after 3400 sensor ingestions with false signals observed in <2% of ingestions.[27] These sensors may be most effective where there is the greatest need to monitor compliance, and among patients where medication non-adherence risks adverse outcomes. Such scenarios include monitoring adherence

to diuretic and β-blocker therapy among HF patients at high risk for readmissions, anticoagulation therapy among atrial fibrillation patients at increased risk for bleeding or thromboembolic complications, and to reduce the risk of stent thrombosis among those receiving dual antiplatelet therapy.

The digital patient

Will patients use and engage with mHealth devices? As clinicians are well aware, changing patient behaviour and sustaining behavioural changes are exceedingly difficult. An expectation from the use of mHealth is a positive behavioural change resulting from patients actively participating in self-care and shared decision-making.[28,29] Device-related factors including design simplicity and usability are important in determining which technologies may be most effective. Equally important are patient factors including patient selection and motivation towards self-monitoring.[30,31] In our opinion, we can consider four categories of patients who engage with mHealth technologies: the first self-select as high-efficiency utilizers, those who are predetermined to modify their behaviours and where devices largely become a bystander in the positive behavioural change; the second are initial adopters but rapidly decline and do not retain device use; the third do not adopt; and the fourth demonstrate a change as the underlying condition, and symptoms improve resulting from modifying behaviours and treatments enabled by device use. The ultimate goal of mHealth is to transition Category 2 and 3 patients to Category 4.

Telemedicine and patient self-measurements

Several studies have demonstrated important observations of mHealth and telemedicine across various patient populations (*Table 1*). Low cost, and widely accessible interventions including text messaging and smartphone apps are effective strategies to promote smoking cessation[32], as a method to improve medication adherence[33] and are simple interventions to prevent diabetes in at-risk patients,[34] and to improve outcomes among patients with coronary heart disease.[35,36] Self-measurements with mHealth devices have been associated with improvements in blood pressure (mean systolic blood pressure reduction of 3-9 mmHg),[37] and improved glycemic control (mean reduction in HbA1c of 0.1-0.3%)[38] among hypertensive and diabetic patients, respectively, and is associated with an increased activity of 2500 steps/day among individuals using pedometers for a monitoring duration of up to 6 months.[39] Numerous studies evaluating mHealth in patients with cardiac disease, particularly HF, have been conducted over the past decade.[40] Device evolution during this time has permitted the design of telemedicine trials that remotely monitor multiple physiological parameters including blood pressure, weight, and heart rate. The established body of clinical trial data has largely demonstrated a beneficial impact of telemedicine in HF including improved survival and reduced HF-related hospitalization when compared with usual care and scheduled patient follow-up.[40,41] In contrast, some studies have demonstrated no difference on outcomes.[42,43] In the critical analysis of a rapidly evolving field, this difference requires explanation. Since devices are generally used similarly and clinical decisions for the management of HF symptoms are largely standard, this difference may result more from different patient classifications than device-related factors.

Table 1 Select trials investigating an mHealth device, text messaging, or a smartphone health application

Study	Study size	Study population	Digital health technology intervention group	Comparator	Outcomes	Salient findings
Hypertension						
McManus et al.[47] TASMIN-SR Randomized trial UK	552	Hypertensive patients with a history of stroke, coronary heart disease, diabetes, or chronic renal failure	Microlife Watch home-based blood pressure monitoring with medication self-titration	Usual care	12-month difference in systolic blood pressure	Greater systolic blood pressure reduction with self-monitoring and medication titration (mean difference of −9 mmHg, 95% CI 6−13 mmHg)
Magid et al.[48] Randomized trial USA	348	Adult patients with hypertension	Home-based blood pressure monitoring and Heart360 Web-based platform	Usual care	6-month proportion of patients achieving blood pressure target of <140/90	Greater proportion of patients achieving blood pressure reduction with home-based monitoring (54 vs. 35%, $P < 0.001$) and a mean reduction in systolic blood pressure of 12 mmHg (95% CI −16 to −9 mmHg)
Diabetes						
Ramachandran et al.[34] Randomized trial India	537	Adult men with impaired glucose tolerance	Text messaging to promote exercise and dietary habits	Usual care	2-year incidence of biochemically proven type 2 diabetes	Lower incidence of type 2 diabetes in the text messaging group than in controls [(18 vs. 27%) hazard ratio 0.64 (95% CI 0.45−0.92), $P = 0.015$]
Quinn et al.[68] Mobile Diabetes Intervention Study Cluster randomized trial USA	163	Adult patients with type II diabetes and HbA1c ≥ 7.5%	Smartphone diabetes application for medication reconciliation and self-care measures as well as clinical decision support	Usual care	Glycaemic control and HbA1c at 12 months	Greater reduction in HbA1c with smartphone application and clinical decision support (−1.9 vs. −0.7%, $P < 0.001$)
Holmen et al.[46] RENEWING HEALTH Randomized trial	151	Adult patients with type II diabetes	Few touch smartphone application	Usual care	Glycaemic control and HbA1c at 4 months	No difference in HbA1c glycaemic control
Cardiac arrest						
Ringh et al.[69] Randomized trial Sweden	9928	Lay volunteers trained in cardiopulmonary resuscitation	Mobile-phone positioning system activated upon notification of an out-of-hospital cardiac arrest and emergency medical services. Simultaneous notification sent to nearby volunteers	Text message or phone call notification not delivered to control group volunteers	Bystander-initiated cardiopulmonary resuscitation before arrival of emergency medical services	The primary outcome measure of bystander-initiated cardiopulmonary resuscitation was significantly higher in the intervention group than in the control group (62 vs. 48%, $P < 0.001$)

Heart failure

Koehler et al.[42] TIM-HF Randomized trial Germany	710	Ambulatory class II–III HF patients with ejection fraction ≤35%	Weight scale, blood pressure, and single lead ECG	Usual care	Composite outcome of hospital admission for HF and/or all-cause mortality at 24 months	No significant difference in outcomes of mortality or HF hospitalization [(15 vs. 17%) hazard ratio 0.89 (95% CI 0.67–1.19, $P = 0.44$)]
Weintraub et al.[41] SPAN-CHF II Randomized trial USA	188	Symptomatic HF patients with a prior hospitalization within 2 weeks	Weight scale, blood pressure, and heart rate monitor	Usual care	HF readmission at 3 months	At 3 months, telemedicine interventions were associated with a reduction in HF readmission [(10 vs. 19%) hazard ratio 0.50 (95% CI 0.25–0.99, $P = 0.05$)]

Cardiac surgery

Cook et al.[70] Prospective observational USA	149	Adult patients >50 years of age undergoing cardiac or vascular surgery	Wireless activity monitor	–	Relationship between activity and post-operative length of stay	Patients with a shorter length of stay were associated with a greater number of steps compared with patients with longer length of stay (818 vs. 223 steps/day, $P < 0.001$)

Arrhythmia

Barrett et al.[71] Prospective observational USA	146	Patients referred cardiac arrhythmia management	Zio Patch wireless telemetry monitor	Simultaneous Holter monitor	Comparison of the arrhythmia detection over the total wear time	Zio Patch detected significantly more events over the total wear time compared with Holter monitoring (96 vs. 61 events, $P < 0.001$)
Lowres et al.[72] SEARCH-AF Prospective observational Australia	1000	Patients aged 65 or greater screened for the presence of an atrial arrhythmia	AliveCor smartphone iECG	–	Prevalence of newly diagnosed atrial fibrillation	Smartphone rhythm screening by pharmacists demonstrated a 7% prevalence and a 1.5% incidence of newly diagnosed atrial fibrillation in a community cohort of elderly patients

Coronary heart disease

Chow et al.[33] TEXT ME Randomized trial Australia	710	Adult patients with coronary heart disease established by a prior history of a myocardial infarction or angiographically proven	Text messaging to promote tobacco abstinence, healthy eating, and maintaining physical activity	Usual care	6-month LDL-C levels, systolic blood pressure, body mass index, physical activity, and smoking status	At 6 months, text messaging was associated with a lower LDL-C (−5 mg/dL), a greater reduction in systolic blood pressure (−7.6 mmHg), a lower body mass index (−1.3), increases in physical activity (+2.93 metabolic equivalents), and a significant reduction in smoking (26 vs. 44%) compared with controls

Continued

Table 1 *Continued*

Study	Study size	Study population	Digital health technology intervention group	Comparator	Outcomes	Salient findings
Cardiac rehabilitation						
Varnfield et al.[73] Randomized trial Australia	120	Patients with a recent myocardial infarction	Smartphone-based home services including health and exercise monitoring	Usual care	6-month adherence to cardiac rehabilitation programmes, 6-min walk test, and quality-of-life assessments	Smartphone-based interventions were associated with a greater adherence (94 vs. 68%) and completion (80 vs. 47%) to rehabilitation programmes and a greater improvement in quality of life than controls. No difference in 6-min walk distance
Chronic diseases						
Steventon et al.[52] Whole Systems Demonstrator Cluster randomized trial UK	3230	Adults with diabetes, HF, or chronic pulmonary diseases	Telehealth devices including weight scales, glucometers, and pulse oxymeters	Usual care	12-month hospital admission and/or mortality	Telehealth was associated with a 18% lower risk of hospital admissions (odds ratio 0.82, 95% CI 0.7–0.97, $P = 0.017$) and 46% lower risk of death (odds ratio 0.54, 95% CI 0.39–0.75, $P < 0.001$)
Healthy lifestyle						
Mattila et al.[54] Randomized trial Finland	114	Healthy adults	Technology toolbox—weight scales, blood pressure monitors, pedometers, wellness diary, and online food log	Usual employee wellness information	Percentage of sustained use at 6 months Changes in weight, blood pressure, and fasting lipid profile	30% sustained use at 6 months Overall, no significant difference in weight, blood pressure, or fasting lipid profile between groups. Weight, body fat, and body mass index decreased in sustained users when compared with non-sustained users
Laing et al.[49] mFit trial Randomized trial USA	212	Patients with a body mass index >25 kg/m^2	MyFitness Pal Smartphone Application	Usual care	Changes in weight and blood pressure at 6 months	No significant difference in weight [(mean group difference −0.3 kg (95% CI −1.5 to 1.0 kg, $P = 0.63$)] or blood pressure [(mean group difference −1.7 mmHg (95% CI −7.1 to 3.8 mmHg, $P = 0.55$)] between groups
Smoking cessation						
Free et al.[32] txt2stop trial Randomized trial UK	5800	Adult smokers aged 16 or greater	Text messaging to promote smoking cessation using motivational messages and behavioural change support	Text messaging unrelated to smoking cessation	6-month outcome of self-reported tobacco abstinence and biochemical verification with salivary cotinine testing	Biochemically verified continuous abstinence at 6 months was greater in the text messaging group than in controls [(10.7 vs. 4.9%) hazard ratio 2.20 (95% CI 1.80–2.68, $P < 0.001$)]

These include elderly patients, those with multiple comorbidities, and patients with advanced disease states where the transmission of surrogate markers of cardiopulmonary pressures such as changes in weight and blood pressure may not reflect minor changes in already elevated filling pressures, or a rapid rise in pressure that prompts symptoms and decompensation.[44,45] Determining a match between patients and digital technologies is necessary to determine the effectiveness of telemedicine and to identify which patients are suitable for device-based self-care. Such circumstances include selecting the appropriate technology that is based on the desired outcome, i.e. glycaemic[46] or blood pressure control,[47,48] weight loss,[49] or for reducing hospital readmissions.[42,43] This match is particularly important when considering remote monitoring among patients with advanced disease states and in scenarios when a healthcare visitation may be more important than telemedicine and device-based self-measurements.[50]

Digital retention

The efficient use of mHealth devices may occur when used among patients who understand the nuances of electronic technologies including the Internet and smartphones and are able to apply the cross-functionality of one device to another.[51] The Whole Systems Demonstrator randomized trial in the UK investigated the impact of telemedicine among 3000 elderly patients with chronic conditions including pulmonary diseases, HF, and diabetes on health-related outcomes. Over a 12-month monitoring period, telemedicine interventions with various mHealth and home-based monitoring devices were associated with improved survival and a lower probability of a hospitalization when compared with standard care (*Table 1*).[52] Despite these positive findings, the investigators reported recruitment challenges with ~40% of the 9000 eligible patients refusing enrolment and identified important patient-related reasons for non-participation and trial withdrawal, including a concern for the technical competence for operation of mHealth devices and a perception that device-based self-care will replace usual face-to-face visitations.[53]

The duration of remote monitoring and digital retention are important factors when considering the time required to sustain long-term behavioural changes and to achieve risk reduction in conditions such as hypertension and diabetes. In this context, Mattila *et al.* have provided important insights of the perceptions of mHealth and assessed the patterns of device use among a heterogeneous group of individuals seeking health improvements.[54] Multiple digital tools including pedometers, weight scales, blood pressure devices, calorie counters, and Web-based programmes were assessed in a randomized trial comparing usual wellness programmes (*n* = 116) with mHealth interventions (*n* = 118) on health-related outcomes. Participants underwent testing such as body fat, aerobic fitness, and cholesterol testing at regular intervals for 1 year. Throughout the trial >75% of participants continued to state a beneficial effect of mHealth on weight loss and physical activity. Despite these positive perceptions, an early and rapid attrition in device use was observed with <50% of participants continuing to use a device at 3 months leading to a very low digital retention rate of 30% at 6 months (*Figure 3*). The dichotomy between high perceived utility and low sustained use presents a significant challenge to promote digital retention and may result from a lack

of understanding of the requirements for self-monitoring, as well as device fatigue through repetitive use of the same technologies over time.

The digital clinic

How can we generate mHealth data, analyse it so that it is clinically meaningful, and integrate it within clinical workflows? Each component of this question is important, and while there has been progress there are not conclusive answers. Several approaches exist to generate mHealth data. One involves precision and personalized care. The other incorporates population-based approaches and device use in new patient populations.
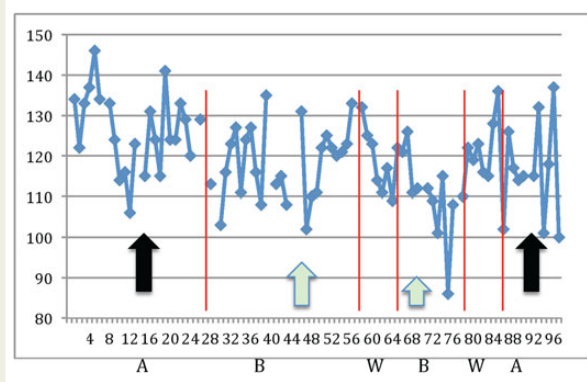
Precision-based mHealth and N-of-1 designs

To generate data in a field with a short duration for technology turnover, mHealth clinical trials are challenged to generate data in a time-efficient fashion and where the lengthy process from study design to execution may be surpassed by new technologies prior to the generation of trial results.[3] By design, the 'N-of-1' trial uses the patient as his or her own control and obtains multiple repeated measurements to determine the optimal response to a particular treatment or intervention.[55] Not all conditions are suitable for N-of-1 designs including monitoring individuals at risk for a myocardial infarction where acute and rapid changes are often preceded by a long periods of clinical stability. In contrast, chronic conditions such as hypertension, diabetes, and HF may be ideally suited and where physiological parameters of blood pressure, glucose, and weight are easily measurable and frequently change in a short period of time. *Figure 4* illustrates a practical example of an N-of-1 design in a patient with hypertension. With the aid of frequent blood pressure measurements, we are able to visualize the blood pressure response to two different classes of antihypertensive medications, the washout and carry-over periods, and ultimately which medication may be
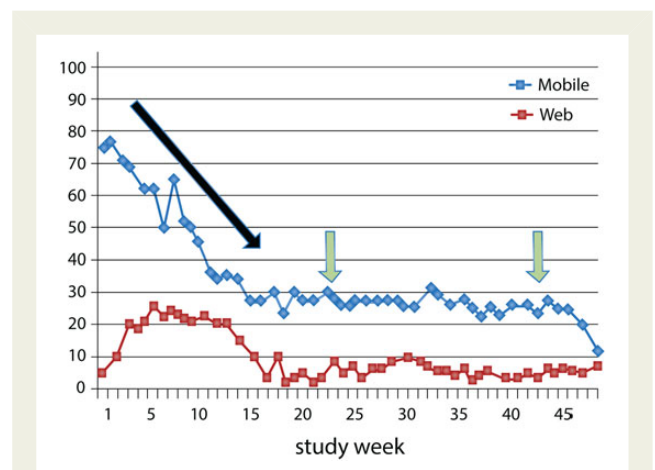
Figure 3 mHealth digital retention. A rapid and early attrition to device use (black arrow) and a low digital retention (green arrows) of 30% at 6 months with mHealth-based self-monitoring. Web denotes online and Internet-based platforms for health and fitness management. Reprinted and modified with permission from Mattila *et al.*[54]

Figure 4 N-of-1 design and precision-based mHealth. (A and B) Denote different antihypertensive drug classes. Drug B (green arrows) lowers blood pressure more than drug A (black arrows). W denotes washout period and the x- and y-axes are the time (in days) and blood pressure (in mmHg), respectively. Figure courtesy of Nicholas Schork PhD and modified with permission.

best targeted for an individualized drug response. On one hand, the strengths of such designs include an individualized approach to treatments, and to quantify disease trends with multiple repeated measures that were previously unidentifiable.[56] On the other hand, tracking minor variations may reveal sub-clinical changes that do not require interventions. The clinician must remain cognisant of noise signals and artefacts observed on mHealth devices that may result in false-positive findings, alarms, and misinterpretations when performed in real-world settings.[55]

**Population-based mHealth in resource-limited areas**
The mHealth advances to improve outcomes and decrease costs in the healthcare systems of industrialized nations must coincide with the efforts to improve healthcare delivery in resource-limited areas. Innovative designs are required to address the rising burden of cardiovascular diseases in developing countries that require cost-efficient and scalable solutions.[57] Smartphone and app-based medication adherence and lifestyle modification intervention were recently reported in the SimCard (Simplified Multifaceted Management Program for Individuals at High Cardiovascular Risk) trial that enrolled adults with atherosclerotic cardiovascular disease in rural Tibet and India.[58] Twenty-three clinical sites (n = 1095 participants) randomized to an electronic decision support system powered by Android[TM] devices and used by community health workers at the point-of-care demonstrated a 17 and 25% increased rate of adherence to antihypertensive therapy and aspirin, respectively, when compared with clinics randomized to usual care (n = 991 participants). Timely healthcare access for conditions such as an acute coronary syndrome remains a challenge in resource-constrained areas. The design of electronic-ICUs in such regions to remotely diagnose and monitor individuals with a myocardial infarction have been associated with marked improvements in the process of STEMI care with a 60% reduction in door-to-needle time that subsequently lead to a >70% improvement in survival.[59]

Ubiquitous use of cellular and Internet technologies in developing nations has permitted the design of 'telecardiology' programmes with cloud computing—the sharing of information on Web-based platforms—and was first investigated in the seminal ASE-REWARD (American Society of Echocardiography: Remote Echocardiography with Web-Based Assessments for Referrals at a Distance) study. Performed within a 2-day period, >1000 patients with symptoms of cardiac disease were imaged with handheld ultrasound in a remote part of India.[60] The echocardiographic studies were uploaded to a cloud-based server and distributed to 75 cardiologists scattered over 60 medical centres in four countries. Scans were uploaded within 4 min and interpreted by the global consortium of readers within 12 h. Results identifying complex structural heart disease were delivered back to the local clinicians effectively creating a digital platform for providing specialty cardiology services where it may be required the most. Among the various design features of mHealth devices, the portability, ease of use, and lower cost are among the features ideally suited for use in resource-limited areas. To assess the benefit of multiple mHealth devices, we have recently initiated the ASE-VALUES (Valvular Assessments Leading to Unexplored Echocardiographic Stratagems) randomized trial in India to evaluate the effectiveness of mHealth-derived assessments including cardiac rhythm, structural abnormalities, exercise capacity, and laboratory testing with point-of-care iECG, handheld echocardiography, activity monitoring, and lab-on-a-chip devices for predicting outcomes among patients with rheumatic heart disease and aims to advance the standard-of-care in the region.

mHealth regulation and integration
Whether in a fee-for-service or a national health system, the perceptions by medical, governmental, and financial institutions have largely supported the concept that mHealth can address the growing demands of an ageing population and rising healthcare costs (https://ec.europa.eu/digital-agenda/en/news/green-paper-mobile-health-mhealth).[61] Several concerns have been raised into the approval of technologies that have not included outcomes data, and we are learning that some health-related apps and devices may not work adequately in the real world.[62,63] Seminal observations have emerged into the high cost of care with mHealth in a unified health system where telemedicine interventions significantly exceeded the threshold for cost-effectiveness by £60 000 per quality-adjusted-life-year among elderly patients with common chronic conditions.[64] Regulatory frameworks have been developed by the US-FDA[65] and the EU-MDD (http://www.mdss.com/pdf/MDD93_42EEC.pdf, https://webstore.iec.ch/preview/info_iec62304%7Bed1.0%7Den_d.pdf) to harmonize new technology approvals; however, key challenges exist between fostering new innovations that are aligned with public health objectives to improve outcomes and reduce costs.

The eHealth Action Plan 2012–20 commissioned by the EU aims to determine the present challenges for mHealth across several domains including research and development, promoting international cooperation, achieving wider interoperability, and harnessing these findings to develop new health technology regulation and future legislation (http://ec.europa.eu/health/ehealth/docs/com_2012_736_en.pdf). One specific mandate is to address the unknown mechanisms necessary to develop data integration and the interoperability of mHealth within large volumes of existing patient data in
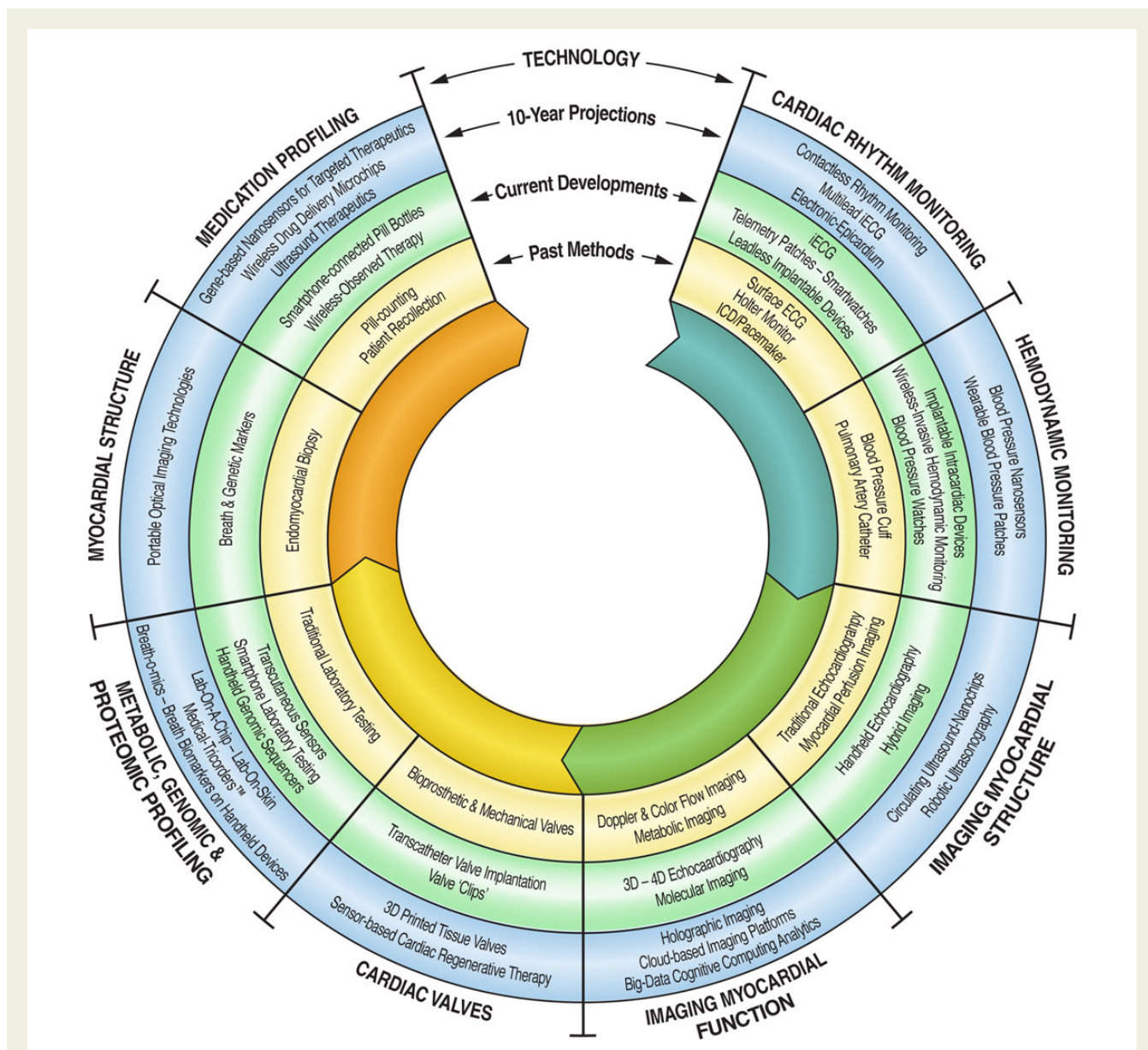
Figure 5 Future mobile and digital health technologies.

national electronic health records (EHRs). Many health-related apps and mHealth devices are programmed to integrate within existing EHRs; however, few if any have achieved this.[66] It is largely unclear how we should develop the resources necessary for administrating digital health services, and the requirement for healthcare personnel to monitor the wave of incoming patient-generated data. To address the integration challenges, Redfern *et al.* recently initiated the CON-NECT (Consumer Navigation of Electronic Cardiovascular Tools) randomized study that is designed to investigate whether a digital health strategy of a smartphone-based app that provides patients with clinical decision support and counselling tools reduces risk in 2000 individuals with cardiovascular disease. Executed in single health system in Australia, the study aims to determine the acceptability and cost-effectiveness of this connected-care strategy.[67] As digital health technologies evolve and become increasingly more available, we must remain vigilant towards monitoring the effectiveness of mHealth and its integration within day-to-day practices.

Healthcare's digital future

Within the next decade, we predict the development of new technologies across several areas in diagnostics, imaging, and therapeutics (*Figure 5*). Similar to clinical practice, the reality of mHealth is becoming increasingly complex. Our analysis of the current state of the field provides three main paths for translating mHealth to the real world: to identify new methods for patient engagement that results in beneficial and measurable behavioural changes, to develop the necessary tools to streamline clinical integration and data analytics, and to outline the regulatory factors that promote the most effective and robust technologies for clinical use. To achieve

all three, we are collectively required to create an evidence base that assesses the impact of mHealth on healthcare quality, cost, and outcomes. In doing so, this interplay of digital devices, digital patients, and digital doctors holds exceptional promise for the future developments in medicine.

Supplementary material

Authors' contributions

S.P.B., J.N., and P.P.S. conceived and designed the research, drafted the manuscript, and made critical revision of the manuscript for key intellectual content.

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References

1. Moore GE. Cramming more components onto integrated circuits. *Electronics* 1965; **38**:114–117.
2. Topol EJ. Transforming medicine via digital innovation. *Sci Transl Med* 2010;**2**:16.
3. Topol EJ, Steinhubl SR, Torkamani A. Digital medical tools and sensors. *JAMA* 2015; **313**:353–354.
4. Kumar S, Nilsen WJ, Abernethy A, Atienza A, Patrick K, Pavel M, Riley WT, Shar A, Spring B, Spruijt-Metz D, Hedeker D, Honavar V, Kravitz R, Lefebvre RC, Mohr DC, Murphy SA, Quinn C, Shusterman V, Swendeman D. Mobile health technology evaluation: the mHealth evidence workshop. *Am J Prev Med* 2013;**45**:228–236.
5. Silva BM, Rodrigues JJ, de la Torre Díez I, López-Coronado M, Saleem K. Mobile-health: a review of current state in 2015. *J Biomed Inform* 2015;**56**:265–272.
6. IMS Institute for Healthcare Informatics. Patient apps for improved healthcare: from novelty to mainstream. **http://www.imshealth.com/deployedfiles/ imshealth/Global/Content/Corporate/IMS%20Health%20Institute/ Reports/Patient_Apps/IIHI_Patient_Apps_Report.pdf** (2013).
7. **http://www.imedicalapps.com/2013/07/apple-android-medical-app/** **(March 2015)**.
8. Walsh JA III, Topol EJ, Steinhubl SR. Novel wireless devices for cardiac monitoring. *Circulation* 2014;**130**:573–581.
9. Kamel H. Heart-rhythm monitoring for evaluation of cryptogenic stroke. *N Engl J Med* 2014;**370**:2532–2533.
10. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, Lindborg K, Brachmann J, CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478–2486.
11. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M, Laupacis A, Côté R, Sharma M, Blakely JA, Shuaib A, Hachinski V, Coutts SB, Sahlas DJ, Teal P, Yip S, Spence JD, Buck B, Verreault S, Casaubon LK, Penn A, Selchen D, Jin A, Howse D, Mehdiratta M, Boyle K, Aviv R, Kapral MK, Mamdani M, EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;**370**: 2467–2477.
12. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, Lau CP, Fain E, Yang S, Bailleul C, Morillo CA, Carlson M, Themeles E, Kaufman ES, Hohnloser SH, ASSERT Investigators. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–129.
13. Saxon LA, Smith A, Doshi S. iPhone rhythm strip—the implications of wireless and ubiquitous heart rate monitoring. *J Am Coll Cardiol* 2012;**59**:E726.
14. Tarakji KG, Wazni OM, Callahan T, Kanj M, Hakim AH, Wolski K, Wilkoff BL, Saliba W, Lindsay BD. Using a novel wireless system for monitoring patients after the atrial fibrillation ablation procedure: the iTransmit study. *Heart Rhythm* 2015;**3**: 554–559.
15. Muhlestein JB, Le V, Albert D, Moreno FL, Anderson JL, Yanowitz F, Vranian RB, Barsness GW, Bethea CF, Severance HW, Ramo B, Pierce J, Barbagelata A, Muhlestein JB. Smartphone ECG for evaluation of STEMI: results of the ST LEUIS Pilot Study. *J Electrocardiol* 2015;**48**:249–259.
16. Williams B, Lacy PS, Baschiera F, Brunel P, Düsing R. Novel description of the 24-hour circadian rhythms of brachial versus central aortic blood pressure and the impact of blood pressure treatment in a randomized controlled clinical trial: the Ambulatory Central Aortic Pressure (AmCAP) Study. *Hypertension* 2013;**61**: 1168–1176.
17. Facchinetti A, Del Favero S, Sparacino G, Castle JR, Ward WK, Cobelli C. Modeling the glucose sensor error. *IEEE Trans Biomed Eng* 2014;**61**:620–629.
18. Del Favero S, Facchinetti A, Sparacino G, Cobelli C, AP@home consortium. Retrofitting of continuous glucose monitoring traces allows more accurate assessment of glucose control in outpatient studies. *Diabetes Technol Ther* 2015;**17**:355–363.
19. Kovatchev BP, Renard E, Cobelli C, Zisser HC, Keith-Hynes P, Anderson SM, Brown SA, Chernavvsky DR, Breton MD, Mize LB, Farret A, Place J, Bruttomesso D, Del Favero S, Boscari F, Galasso S, Avogaro A, Magni L, Di Palma F, Toffanin C, Messori M, Dassau E, Doyle FJ III. Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas. *Diabetes Care* 2014;**37**:1789–1796.
20. Chen LY, Tee BC, Chortos AL, Schwartz G, Tse V, Lipomi DJ, Wong HS, McConnell MV, Bao Z. Continuous wireless pressure monitoring and mapping with ultra-small passive sensors for health monitoring and critical care. *Nat Commun* 2014;**5**:5028.
21. Gurun G, Tekes C, Zahorian J, Xu T, Satir S, Karaman M, Hasler J, Degertekin FL. Single-chip CMUT-on-CMOS front-end system for real-time volumetric IVUS and ICE imaging. *IEEE Trans Ultrason Ferroelectr Freq Control* 2014;**61**:239–250.
22. Lau CP, Siu CW, Tse HF. Future of implantable devices for cardiac rhythm management. *Circulation* 2014;**129**:811–822.
23. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS, CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial. *Lancet* 2011;**377**:658–666.
24. Adamson PB, Abraham WT, Bourge RC, Costanzo MR, Hasan A, Yadav C, Henderson J, Cowart P, Stevenson LW. Wireless pulmonary artery pressure monitoring guides management to reduce decompensation in heart failure with preserved ejection fraction. *Circ Heart Fail* 2014;**7**:935–944.
25. Baroletti S, Dell'Orfano H. Medication adherence in cardiovascular disease. *Circulation* 2010;**121**:1455–1458.
26. DiCarlo L, Moon G, Intondi A, Duck R, Frank J, Hafazi H, Behzadi Y, Robertson T, Costello B, Savage G, Zdeblick M. Digital health solution for using and managing medications: wirelessly observed therapy. *IEEE Pulse* 2012;**3**:23–26.
27. Au-Yeung KY, Moon GD, Robertson TL, Dicarlo LA, Epstein MS, Weis SE, Reves RR, Engel G. Early clinical experience with networked system for promoting patient self-management. *Am J Manag Care* 2011;**17**:e277–e287.
28. Patel MS, Asch DA, Volpp KG. Wearable devices as facilitators, not drivers, of health behavior change. *JAMA* 2015;**313**:459–460.
29. Jain SH, Powers BW, Hawkins JB, Brownstein JS. The digital phenotype. *Nat Biotechnol* 2015;**33**:462–463.
30. de Jongh T, Gurol-Urganci I, Vodopivec-Jamsek V, Car J, Atun R. Mobile phone messaging for facilitating self-management of long-term illnesses. *Cochrane Database Syst Rev* 2012;**12**:CD007459.
31. Castelnuovo G, Zoppis I, Santoro E, Ceccarini M, Pietrabissa G, Manzoni GM, Corti S, Borrello M, Giusti EM, Cattivelli R, Melesi A, Mauri G, Molinari E, Sicurello F. Managing chronic pathologies with a stepped mHealth-based approach in clinical psychology and medicine. *Front Psychol* 2015;**6**:407.
32. Free C, Knight R, Robertson S, Whittaker R, Edwards P, Zhou W, Rodgers A, Cairns J, Kenward MG, Roberts I. Smoking cessation support delivered via mobile phone text messaging (txt2stop): a single-blind, randomised trial. *Lancet* 2011;**378**: 49–55.
33. Chow CK, Redfern J, Hillis GS, Thakkar J, Santo K, Hackett ML, Jan S, Graves N, de Keizer L, Barry T, Bompoint S, Stepien S, Whittaker R, Rodgers A, Thiagalingam A. Effect of lifestyle-focused text messaging on risk factor modification in patients with coronary heart disease: a randomized clinical trial. *JAMA* 2015;**314**:1255–1263.

34. Ramachandran A, Snehalatha C, Ram J, Selvam S, Simon M, Nanditha A, Shetty AS, Godsland IF, Chaturvedi N, Majeed A, Oliver N, Toumazou C, Alberti KG, Johnston DG. Effectiveness of mobile phone messaging in prevention of type 2 diabetes by lifestyle modification in men in India: a prospective, parallel-group, randomised controlled trial. *Lancet Diabetes Endocrinol* 2013;**1**:191–198.

35. Neubeck L, Lowres N, Benjamin EJ, Freedman SB, Coorey G, Redfern J. The mobile revolution-using smartphone apps to prevent cardiovascular disease. *Nat Rev Cardiol* 2015;**12**:350–360.

36. Piette JD, List J, Rana GK, Townsend W, Striplin D, Heisler M. Mobile health devices as tools for worldwide cardiovascular risk reduction and disease management. *Circulation* 2015;**132**:2012–2027.

37. Uhlig K, Patel K, Ip S, Kitsios GD, Balk EM. Self-measured blood pressure monitoring in the management of hypertension: a systematic review and meta-analysis. *Ann Intern Med* 2013;**159**:185–194.

38. Poolsup N, Suksomboon N, Kyaw AM. Systematic review and meta-analysis of the effectiveness of continuous glucose monitoring (CGM) on glucose control in diabetes. *Diabetol Metab Syndr* 2013;**5**:39.

39. Bravata DM, Smith-Spangler C, Sundaram V, Gienger AL, Lin N, Lewis R, Stave CD, Olkin I, Sirard JR. Using pedometers to increase physical activity and improve health: a systematic review. *JAMA* 2007;**298**:2296–2304.

40. Inglis SC, Clark RA, McAlister FA, Stewart S, Cleland JG. Which components of heart failure programmes are effective? A systematic review and meta-analysis of the outcomes of structured telephone support or telemonitoring as the primary component of chronic heart failure management in 8323 patients: abridged Cochrane review. *Eur J Heart Fail* 2011;**13**:1028–1040.

41. Weintraub A, Gregory D, Patel AR, Levine D, Venesy D, Perry K, Delano C, Konstam MA. A multicenter randomized controlled evaluation of automated home monitoring and telephonic disease management in patients recently hospitalized for congestive heart failure: the SPAN-CHF II trial. *J Card Fail* 2010;**16**:285–292.

42. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Böhm M, Boll H, Baumann G, Honold M, Koehler K, Gelbrich G, Kirwan BA, Anker SD, Telemedical Interventional Monitoring in Heart Failure Investigators. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. *Circulation* 2011;**123**:1873–1880.

43. Lyngå P, Persson H, Hägg-Martinell A, Hägglund E, Hagerman I, Langius-Eklöf A, Rosenqvist M. Weight monitoring in patients with severe heart failure (WISH): a randomized controlled trial. *Eur J Heart Fail* 2012;**14**:438–444.

44. Bhavnani S, Waalen J, Srivastava A, Heywood JT. Which patients? Which devices? mHealth monitoring with wearable and implantable devices in heart failure: meta analysis of randomized trials. *J Am Coll Cardiol* 2015;**65**. doi:10.1016/S0735-1097(15)61030-0.

45. Stevenson LW, Zile M, Bennett TD, Kueffer FJ, Jessup ML, Adamson P, Abraham WT, Manda V, Bourge RC. Chronic ambulatory intracardiac pressures and future heart failure events. *Circ Heart Fail* 2010;**3**:580–587.

46. Holmen H, Torbjørnsen A, Wahl AK, Jenum AK, Småstuen MC, Arsand E, Ribu L. A mobile health intervention for self-management and lifestyle change for persons with type 2 diabetes, Part 2: one-year results from the Norwegian randomized controlled trial RENEWING HEALTH. *JMIR Mhealth Uhealth* 2014;**2**:e57.

47. McManus RJ, Mant J, Haque MS, Bray EP, Bryan S, Greenfield SM, Jones MI, Jowett S, Little P, Penaloza C, Schwartz C, Shackleford H, Shovelton C, Varghese J, Williams B, Hobbs FD, Gooding T, Morrey I, Fisher C, Buckley D. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. *JAMA* 2014;**312**:799–808.

48. Magid DJ, Olson KL, Billups SJ, Wagner NM, Lyons EE, Kroner BA. A pharmacist-led, American Heart Association Heart360 Web-enabled home blood pressure monitoring program. *Circ Cardiovasc Qual Outcomes* 2013;**6**:157–163.

49. Laing BY, Mangione CM, Tseng CH, Leng M, Vaisberg E, Mahida M, Bholat M, Glazier E, Morisky DE, Bell DS. Effectiveness of a smartphone application for weight loss compared with usual care in overweight primary care patients: a randomized, controlled trial. *Ann Intern Med* 2014;**161**:S5–S12.

50. Takahashi PY, Pecina JL, Upatising B, Chaudhry R, Shah ND, Van Houten H, Cha S, Croghan I, Naessens JM, Hanson GJ. A randomized controlled trial of telemonitoring in older adults with multiple health issues to prevent hospitalizations and emergency department visits. *Arch Intern Med* 2012;**172**:773–779.

51. Bujnowska-Fedak MM, Mastalerz-Migas A. Usage of medical Internet and e-health services by the elderly. *Adv Exp Med Biol* 2015;**834**:75–80.

52. Steventon A, Bardsley M, Billings J, Dixon J, Doll H, Hirani S, Cartwright M, Rixon L, Knapp M, Henderson C, Rogers A, Fitzpatrick R, Hendy J, Newman S. Effect of telehealth on use of secondary care and mortality: findings from the Whole System Demonstrator cluster randomised trial. *BMJ* 2012;**344**:e3874.

53. Sanders C, Rogers A, Bowen R, Bower P, Hirani S, Cartwright M, Fitzpatrick R, Knapp M, Barlow J, Hendy J, Chrysanthaki T, Bardsley M, Newman SP. Exploring barriers to participation and adoption of telehealth and telecare within the Whole System Demonstrator trial: a qualitative study. *BMC Health Serv Res* 2012;**12**:220.

54. Mattila E, Orsama AL, Ahtinen A, Hopsu L, Leino T, Korhonen I. Personal health technologies in employee health promotion: usage activity, usefulness, and health-related outcomes in a 1-year randomized controlled trial. *JMIR Mhealth Uhealth* 2013;**1**:e16.

55. Lillie EO, Patay B, Diamant J, Issell B, Topol EJ, Schork NJ. The n-of-1 clinical trial: the ultimate strategy for individualizing medicine? *Per Med* 2011;**8**:161–173.

56. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med* 2015;**372**:793–795.

57. Yusuf S, Rangarajan S, Teo K, Islam S, Li W, Liu L, Bo J, Lou Q, Lu F, Liu T, Yu L, Zhang S, Mony P, Swaminathan S, Mohan V, Gupta R, Kumar R, Vijayakumar K, Lear S, Anand S, Wielgosz A, Diaz R, Avezum A, Lopez-Jaramillo P, Lanas F, Yusoff K, Ismail N, Iqbal R, Rahman O, Rosengren A, Yusufali R, Kelishadi R, Kruger A, Puoane T, Szuba A, Chifamba J, Oguz A, McQueen M, McKee M, Dagenais G, PURE Investigators. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *N Engl J Med* 2014;**371**:818–827.

58. Tian M, Ajay VS, Dunzhu D, Hameed SS, Li X, Liu Z, Li C, Chen H, Cho K, Li R, Zhao X, Jindal D, Rawal I, Ali MK, Peterson ED, Ji J, Amarchand R, Krishnan A, Tandon N, Xu LQ, Wu Y, Prabhakaran D, Yan LL. A cluster-randomized, controlled trial of a Simplified Multifaceted Management Program for Individuals at High Cardiovascular Risk (SimCard Trial) in rural Tibet, China, and Haryana, India. *Circulation* 2015;**132**:815–824.

59. Gupta S, Dewan S, Kaushal A, Seth A, Narula J, Varma A. eICU reduces mortality in STEMI patients in resource-limited areas. *Glob Heart* 2014;**9**:425–427.

60. Singh S, Bansal M, Maheshwari P, Adams D, Sengupta SP, Price R, Dantin L, Smith M, Kasliwal RR, Pellikka PA, Thomas JD, Narula J, Sengupta PP, ASE-REWARD Study Investigators. American Society of Echocardiography: Remote Echocardiography with Web-Based Assessments for Referrals at a Distance (ASE-REWARD) Study. *J Am Soc Echocardiogr* 2013;**26**:221–233.

61. Cortez NG, Cohen IG, Kesselheim AS. FDA regulation of mobile health technologies. *N Engl J Med* 2014;**371**:372–379.

62. Semigran HL, Linder JA, Gidengil C, Mehrotra A. Evaluation of symptom checkers for self diagnosis and triage: audit study. *BMJ* 2015;**351**:h3480.

63. Ioannidis JP. Stealth research: is biomedical innovation happening outside the peer-reviewed literature? *JAMA* 2015;**313**:663–664.

64. Henderson C, Knapp M, Fernández JL, Beecham J, Hirani SP, Cartwright M, Rixon L, Beynon M, Rogers A, Bower P, Doll H, Fitzpatrick R, Steventon A, Bardsley M, Hendy J, Newman SP, Whole System Demonstrator Evaluation Team. Cost effectiveness of telehealth for patients with long term conditions (Whole Systems Demonstrator telehealth questionnaire study): nested economic evaluation in a pragmatic, cluster randomised controlled trial. *BMJ* 2013;**346**:f1035.

65. http://docs.house.gov/meetings/IF/IF00/20150519/103516/BILLS-1146ih.pdf (July 2015).

66. Gagnon MP, Ngangue P, Payne-Gagnon J, Desmartis M. m-Health adoption by healthcare professionals: a systematic review. *J Am Med Inform Assoc* 2015; doi: 10.1093/jamia/ocv052.

67. Redfern J, Usherwood T, Harris MF, Rodgers A, Hayman N, Panaretto K, Chow C, Lau AY, Neubeck L, Coorey G, Hersch F, Heeley E, Patel A, Jan S, Zwar N, Peiris D. A randomised controlled trial of a consumer-focused e-health strategy for cardiovascular risk management in primary care: the Consumer Navigation of Electronic Cardiovascular Tools (CONNECT) study protocol. *BMJ Open* 2014;**4**:e004523.

68. Quinn CC, Clough SS, Minor JM, Lender D, Okafor MC, Gruber-Baldini A. WellDoc mobile diabetes management randomized controlled trial: change in clinical and behavioral outcomes and patient and physician satisfaction. *Diabetes Technol Ther* 2008;**10**:160–168.

69. Ringh M, Rosenqvist M, Hollenberg J, Jonsson M, Fredman D, Nordberg P, Järnbert-Pettersson H, Hasselqvist-Ax I, Riva G, Svensson L. Mobile-phone dispatch of laypersons for CPR in out-of-hospital cardiac arrest. *N Engl J Med* 2015;**372**:2316–2325.

70. Cook DJ, Thompson JE, Prinsen SK, Dearani JA, Deschamps C. Functional recovery in the elderly after major surgery: assessment of mobility recovery using wireless technology. *Ann Thorac Surg* 2013;**96**:1057–1061.

71. Barrett PM, Komatireddy R, Haaser S, Topol S, Sheard J, Encinas J, Fought AJ, Topol EJ. Comparison of 24-hour Holter monitoring with 14-day novel adhesive patch electrocardiographic monitoring. *Am J Med* 2014;**127**:95.e11–e17.

72. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, Bennett AA, Briffa T, Bauman A, Martinez C, Wallenhorst C, Lau JK, Brieger DB, Sy RW, Freedman SB. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost* 2014;**111**:1167–1176.

73. Varnfield M, Karunanithi M, Lee CK, Honeyman E, Arnold D, Ding H, Smith C, Walters DL. Smartphone-based home care model improved use of cardiac rehabilitation in postmyocardial infarction patients: results from a randomised controlled trial. *Heart* 2014;**100**:1770–1779.