ANNUAL REVIEWS

Annual Review of Analytical Chemistry

Wearable and Implantable Sensors for Biomedical Applications

Hatice Ceylan Koydemir[1] and Aydogan Ozcan[1,2]

[1]Electrical and Computer Engineering Department, University of California, Los Angeles, California 90095, USA; email: ozcan@ucla.edu

[2]Bioengineering Department and California NanoSystems Institute (CNSI), University of California, Los Angeles, California 90095, USA

Annu. Rev. Anal. Chem. 2018. 11:6.1–6.20

The *Annual Review of Analytical Chemistry* is online at anchem.annualreviews.org

https://doi.org/10.1146/annurev-anchem-061417-125956

Keywords

wearable sensors, implantable sensors, telemedicine, digital health monitoring, mobile health, biosensors, biomedical applications

Abstract

Mobile health technologies offer great promise for reducing healthcare costs and improving patient care. Wearable and implantable technologies are contributing to a transformation in the mobile health era in terms of improving healthcare and health outcomes and providing real-time guidance on improved health management and tracking. In this article, we review the biomedical applications of wearable and implantable medical devices and sensors, ranging from monitoring to prevention of diseases, as well as the materials used in the fabrication of these devices and the standards for wireless medical devices and mobile applications. We conclude by discussing some of the technical challenges in wearable and implantable technology and possible solutions for overcoming these difficulties.

Review in Advance first posted on February 28, 2018. (Changes may still occur before final publication.)

1. INTRODUCTION

Wearable and implantable devices or electronics have rapidly entered the area of digital health in various biomedical applications, including monitoring, tracking, and recording the vital signs of people with the aim of improving their health and that of their family. Some of these technologies are becoming part of our lives in the form of accessories such as smart watches, armbands, and glasses (1–7). One of the first implantable health devices was created in the 1960s, which was a fully implanted cardiac pacemaker for patients with arrhythmia (1, 7). Since then, improved versions of pacemakers, implantable cardioverter defibrillators (ICDs), and implantable deep brain stimulators have been developed and used as a treatment option for millions of patients (8, 9). These implantable devices are battery powered and composed of programmable circuitry as well as biocompatible electrodes and wires.

Advancements in packaging and fabrication technologies have enabled embedding various microelectronic and micromechanical sensors, such as gyroscopes, accelerometers, and image sensors, into a small area on a rigid or flexible substrate with high sensitivity at a low cost. These advances add various capabilities to wearable and implantable devices, including motion sensing as well as physiological and biochemical sensing (10). Furthermore, mobile devices have been integrated with wireless communication technology since the 1990s, providing data rates of at least 0.2 Mbit/s. According to a recent report of the International Telecommunication Union (ITU) (11), it was estimated that 84% of the world's population (approximately 5.1 billion people) had access to 3G or better mobile broadband coverage by the end of 2016. This ongoing extension of broadband wireless networks into rural areas, even in low- and middle-income countries, opens a new era for wearable and implantable devices and sensors to continuously monitor the health of patients remotely, even in resource-limited settings (12, 13). This is important for reducing healthcare access problems and healthcare-associated costs, which are economic burdens, especially for countries with aging populations.

This article provides a review of the biomedical applications of wearables and implantables, including commercially available devices, emerging developments, technical challenges, certain regulatory issues for wireless medical devices, and future trends. First, we review the physiological parameters monitored and symptoms of diseases tracked using wearable devices. We then review some of the wearable devices worn on different parts of the body, including ingestible and implantable wearables, and the materials used in the fabrication of these devices. Next, we briefly provide information on standards for wireless medical devices and mobile applications regulated by the US Food and Drug Administration (FDA). Finally, technical challenges and future trends are discussed.

2. MONITORING THE USE OF WEARABLES

2.1. Parameters

Advancements in sensor technologies have resulted in a variety of wearable computers and sensors that can be used in either contact or noncontact mode for biomedical applications (**Figure 1**). Several wearable devices are commercially available for monitoring patients' vital signs on a continual basis, which is crucial for modern digital health, and they allow for data transfer between the device and a smartphone or other devices (e.g., those at healthcare units) through Bluetooth, Wi-Fi, or other wireless technologies (14). These devices not only monitor vital signs, but they also measure other parameters from the daily activities of patients to aid in their health status, such as calories burned (15, 16), step monitoring (16), sleep patterns, activity levels (15–17), and eating habits (18). In particular, heart rate, blood oxygen saturation level, body and/or skin temperature,

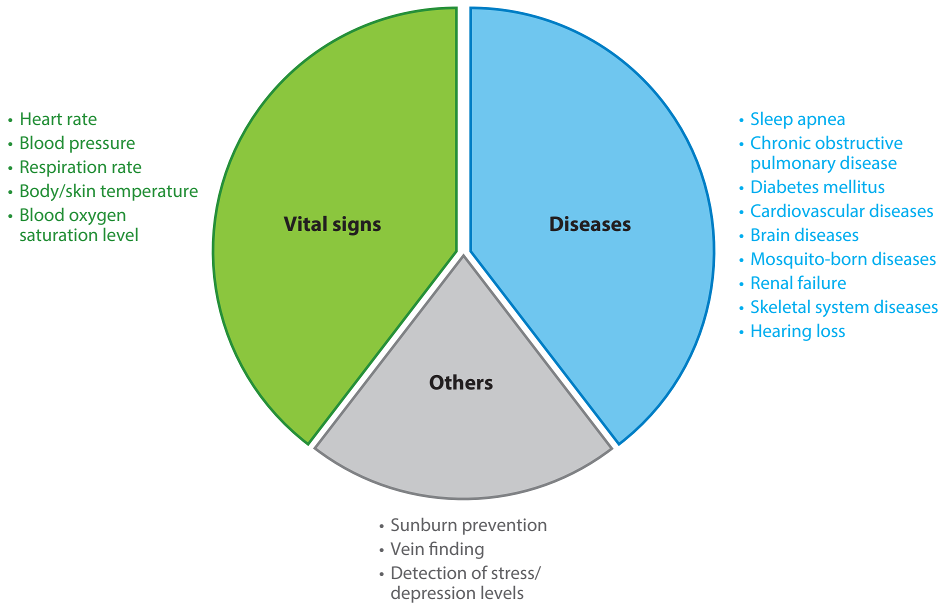

Figure 1

Some biomedical applications of wearables, including those to monitor vital signs, a variety of diseases, and other factors.

respiration rate, and blood pressure are the major physiological parameters that can be monitored using the majority of wearables (**Table 1**).

Heart rate is a commonly measured parameter using wearables, and this vital sign can easily be detected from various body parts (**Figure 2**). The first wireless heart rate wearable, a wristband, was introduced in the 1980s to monitor the real-time performance of athletes during exercise (19). Given the popularity of continuous heart rate monitoring, which is particularly important for fitness-oriented individuals, dozens of wearable models are currently available in the market that can measure the heartbeat rate at rest, as well as during walking and running, from various places on the body, including the ear (15, 16, 20), wrist (17, 21–24), finger (25), and chest (26), by means of optical sensors, gyroscopes, accelerometers, and pressure sensors embedded in the wearables. These devices not only provide the heartbeat rate of users but also time-based plots and recordings of the history together with global positioning systems (GPS) for improved performance analysis (27).

Another vital sign measured by wearables is blood oxygen saturation level, which is a measure of breathing and circulation of blood in the vessels. The normal range for the arterial oxygen level is 75–100 mm Hg, while the range lower than 60 mm Hg indicates the need for supplemental oxygen. It can be measured noninvasively from the ear (16) and fingertip (25) using pulse oximeters integrated into wearables operating with light-emitting diodes (LEDs) at two wavelengths at least (28), where one is less than 810 nm (e.g., 660 nm) and the other is higher than 810 nm (e.g., 1,000 nm) (3). The sequential sampling of light transmitted through the finger or ear is carried out using a photodiode lying on the opposite side of the tissue, which enables determination of the blood oxygen saturation level through a ratiometric analysis of the oxygenated and deoxygenated blood hemoglobin in the presence of a pre-established calibration curve.

Another vital sign of interest for wearables is the body temperature, which is within the range of 36.5°C (97.8°F) to 37.2°C (99°F) for a healthy adult. An increase in body temperature is an

Table 1 Physiological parameters and examples of commercial wearable devices and their sensors

Vital sign	Wearable device	Sensor	Reference
Heart rate	Earring (e.g., Ear-O-Smart)	Pulse oximeter	15
Heart rate	Earpiece (e.g., Cosinuss, one earpiece)	Pulse oximeter	20
Heart rate	Earphone (Bragi)	Pulse oximeter	16
Heart rate	Watch (e.g., Samsung Gear Fit, Basis)	Pulse oximeter	17, 21
Heart rate	Fingertip (e.g., Go2 Fingertip Pulse Oximeter)	Pulse oximeter	25
Heart rate	Sensor patch (Avery Dennison Metria)	Electrocardiogram	135
Heart rate	Wristband (e.g., Phyode W/Me wristband) Wristband (e.g., iHealth, Omron)	Touch-activated electrocardiogram sensor Pressure sensor	22–24
Heart rate	Glass (e.g., Google Glass)	Gyroscope, accelerometer, image sensor	32
Heart rate	Shirt (e.g., PoloTech)	3D accelerometer	26
Blood oxygen saturation level	Earphone (Bragi)	Pulse oximeter	16
Blood oxygen saturation level	Fingertip (e.g., Go2 Fingertip Pulse Oximeter)	Pulse oximeter	25
Body and/or skin temperature	Earpiece (e.g., Cosinuss one earpiece)	Temperature sensor	20
Body and/or skin temperature	Tattoo (e.g., VivaLnk Fever Scout)	Temperature sensor	29
Body and/or skin temperature	Earphone (Bragi)	Temperature sensor	16
Body and/or skin temperature	Watch (e.g., Basis)	Temperature sensor	17
Respiration rate	Belt accessory (e.g., Spire)	Accelerometer	31
Respiration rate	Smart textile electrocardiogram sensor	Piezo-resistive sensor	2
Respiration rate	Glass	Gyroscope, accelerometer, image sensor	32
Blood pressure	Sensor	Two photoplethysmography sensors	None
Blood pressure	Patch	Potential difference	136
Blood pressure	Wristband (e.g., iHealth, Omron)	Pressure sensor	23, 24

important sign that is mostly related to disturbance in the immunological system of patients. It can be measured from the mouth, rectum, eardrum, under the arm, and through the skin. Because the skin temperature is easily affected by external factors, and the temperature control unit of the body is located near the hypothalamus, it is preferable to measure body (core) temperature rather than the skin temperature, which is done from places close to the innermost organs. Unlike heart rate, body temperature is not measured continuously, but at certain time intervals, because the change in body temperature is a slow process. Patches (29), earpieces (20), and watches (17) are typical wearables for measuring body temperature.

Breathing rhythm or respiration rate monitoring is one of the basic methods for determining the health status of a patient when performing clinical evaluations (30). Continuous monitoring of respiration rate can provide information on the progression of an illness such as cardiac arrest (30). There are two modes for measuring breathing rhythm: (*a*) contact mode (2, 31), by means of attaching sensing devices to the bodies of patients, and (*b*) noncontact mode (32), by capturing images of the patients using infrared-based sensors. Patches, bras, shirts, and bracelets are some examples of wearable devices for monitoring respiration rate.

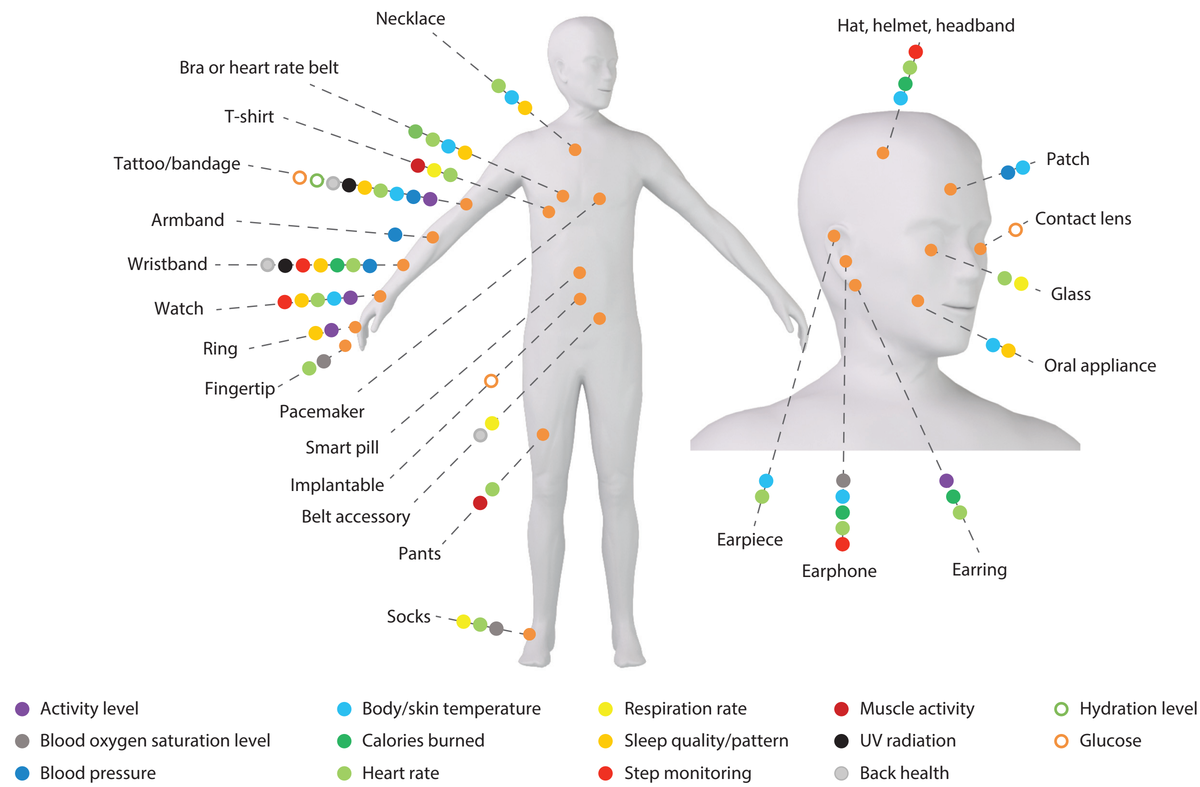

Figure 2

Wearable devices worn on various body parts and the parameters that they can monitor.

Another vital sign is blood pressure, which refers to the pressure of blood in the circulatory system; a pressure less than 120/80 mm Hg is considered normal by clinicians. If the values are +10 higher than normal, this means the patient has prehypertension and needs to begin a treatment program to regain healthy blood pressure levels. High blood pressure levels can be an indicator of damage to artery walls. Therefore, monitoring blood pressure levels can be useful in the prevention and management of high blood pressure. Wearable monitoring devices such as wrist- and arm-based blood pressure monitors are based on noninvasive measurements with skin contact, while avoiding errors due to the movement of patients during measurement.

2.2. Diseases and Disabilities

Mobile technologies are paving the way for revolutionizing the diagnosis of diseases and monitoring patient treatment. Because wearables are personal devices that provide objective and continuous monitoring of vital parameters, they can be used as a clinical tool to determine the patterns of a particular disease, provide an improved understanding of the disease, and monitor the health information of users (1). Although wearables currently on the market are mainly used for general fitness and wellness purposes, various devices are being designed for making a difference in the lives of people by gathering information on a particular disease. In this subsection, we discuss some of these examples in which wearable technologies are used.

2.2.1. Sleep apnea. This extremely common condition results in interruptions or a decrease in breathing for a few seconds up to a minute. It affects approximately 18 million people in the United States alone. The treatment type depends on the severity of the case and ranges from weight loss to surgical operations (33). DentiTrac (34, 35) is an FDA-cleared wearable oral device for following the prescribed therapy for sleep apnea. It measures the temperature, movement, and head position of patients by determining the spatial orientation of the device in the mouth.

2.2.2. Chronic obstructive pulmonary disease. Chronic obstructive pulmonary disease (COPD) is another common lung disease that leads to shortness of breath. It affects 210 million people worldwide and is a major health problem for people 40 years and older (36). Various sensors, including an ear wearable, have been developed to monitor the physical activities of patients with COPD (37–41). These wearables allow patients to continuously evaluate their condition at home, where they are away from most of the air pollutants and bioaerosols associated with healthcare units. Therefore, using wearables for COPD may reduce healthcare costs for patients that can be treated at home (42).

2.2.3. Diabetes mellitus. This is a chronic disease whereby the body cannot produce sufficient insulin, and the control of blood glucose levels is essential for diabetic patients. A wearable artificial pancreas is commercially available for glucose level monitoring and regulation (43). It is composed of a flexible core system as a brain and three wedges for insulin delivery, glucose sensing, and glucagon delivery. Another wearable that is being designed to measure blood sugar levels in diabetics is the smart contact lens that Google/Verily Life Sciences has been developing in collaboration with Novartis (Basel, Switzerland) (1). However, there is very little public domain information about the technical details and feasibility of this approach.

2.2.4. Cardiovascular diseases. This group of diseases is related to the heart and veins, including venous thrombosis, heart failure, and cardiac dysrhythmia. According to a World Health Organization report, more than 17 million patients died from cardiovascular diseases in 2008, and 23 million people are threatened by these diseases each year (44).Various wearable sensors exist for providing real-time heart rate measurements (15–17, 20–26, 32, 45, 46), such as the wireless blood pressure wrist monitor by iHealth (Louisville, KY), which monitors blood pressure in connection with a smartphone (1). Validation of the performance of this wrist monitor was investigated by Wang et al. (47), and it was shown that the accuracy of the measurements was in good agreement with the reference clinical measurements. The standard deviation between the two methods was found to be within ± 7 mm Hg for both systolic blood pressure and diastolic blood pressure (47).

2.2.5. Brain diseases. Dementia refers to a group of brain diseases leading to a decrease in cognitive abilities (48, 49). This group includes Alzheimer's, Huntington's, and Parkinson's diseases (50) as well as vascular dementia (51). The Vega GPS bracelet is a wearable sensor for ensuring the safety of people with Alzheimer's disease by monitoring their location with the use of GPS and global system for mobile communications positioning (52). Epilepsy is another group of brain disorders that causes seizures. Embrace by Empatica (Milan, Italy) is a wristband for monitoring physiological signals in epileptic people in real time to alert others, for example, family members (53).

2.2.6. Mosquito-borne diseases. Mosquitoes cause a wide range of deadly diseases, such as malaria, chikungunya, yellow fever, the Zika virus, and the Ebola virus, which affect millions of people worldwide. The Kite Patch is a patch-type wearable that disperses volatile compounds and is worn on a shirt to repel mosquitoes (54, 55). TermoTell (56) is a bracelet for monitoring the temperature and sweat patterns of a child and sends a notification to the smartphones of its parents if there is a match on the data gathered with malaria symptoms.

2.2.7. Renal failure. This condition is also known as kidney failure and can be categorized as acute kidney injury and chronic kidney disease. In the treatment of renal failure, dialysis is commonly used, in which kidney function is replaced by a machine. To replace dialysis, a wearable artificial kidney has been developed, and its current version weighs only ∼4.5 kg (57).

2.2.8. Skeletal system diseases. Joint disorders, osteoporosis, and poor posture are among the most common skeletal conditions. Using three-dimensional (3D) gyroscopes, accelerometers, and magnetometers embedded into wearable sensors [e.g., CUR Smart Pain Relief (58) and Valedo (59)], the chronic pain resulting from most skeletal diseases can be treated with transcutaneous electrical nerve stimulation and by performing therapeutic exercises. Another wearable, Lumo Lift (60), monitors postural variation and warns users through vibrations when they deviate from normal posture, reminding them to return to a normal posture.

2.2.9. Sunburn prevention. The ultraviolet (UV) radiation of sunlight has harmful effects on the skin, causing wrinkles, burns, aging, and even skin cancer. Approximately three million people per year are diagnosed with skin cancer globally (61). Wearable UV sensors, which can be worn on the arm in the form of a bracelet, armband, or wristband, can be used to monitor UV exposure levels with alerts for potential skin damage and safety precautions, as well as estimating vitamin D production levels.

2.2.10. Vein finding. A wearable smart glass termed Eyes-On technology (62) enables nurses to rapidly see the veins of patients through the skin by incorporating multispectral 3D imaging and wireless connectivity.

2.2.11. Detection of stress/depression levels. Wearables can also be used to determine the state of mind of their users. For example, Airo Health's (Canada) recent product is a wristband that monitors heart rate variability and aims to warn the user about a rise in personal stress levels (63).

3. WEARABLE TECHNOLOGIES FOR DIFFERENT BODY PARTS

Wearable sensors can be worn on the head, body, arm, and leg/foot, or they can be implantable, such as smart pills or artificial organs (see **Figure 2**). The common purpose of all wearable sensors is to provide useful data while the user is wearing the sensors and performing activities such as walking, sleeping, and eating. Most of these sensors record or transfer the user data to mobile devices or smartphones through dedicated applications (**Figure 3**). Starting with the next subsection, we summarize some examples of different body parts for which wearables have been designed.

3.1. Head

The head is the uppermost part of the body and includes the forehead, ears, eyes, nose, and mouth. The wearable health-tracking devices for the head comprise mainly glasses, goggles, contact lenses, hats, headbands, hearing aids, earrings, earphones, and patches.

Modern smart glasses can be considered as wearable computers, and they are embedded with several sensors, such as gyroscopes, accelerometers, pressure sensors, image sensors, and microphones. They can be operated using voice commands through a user interface. Google Glass,

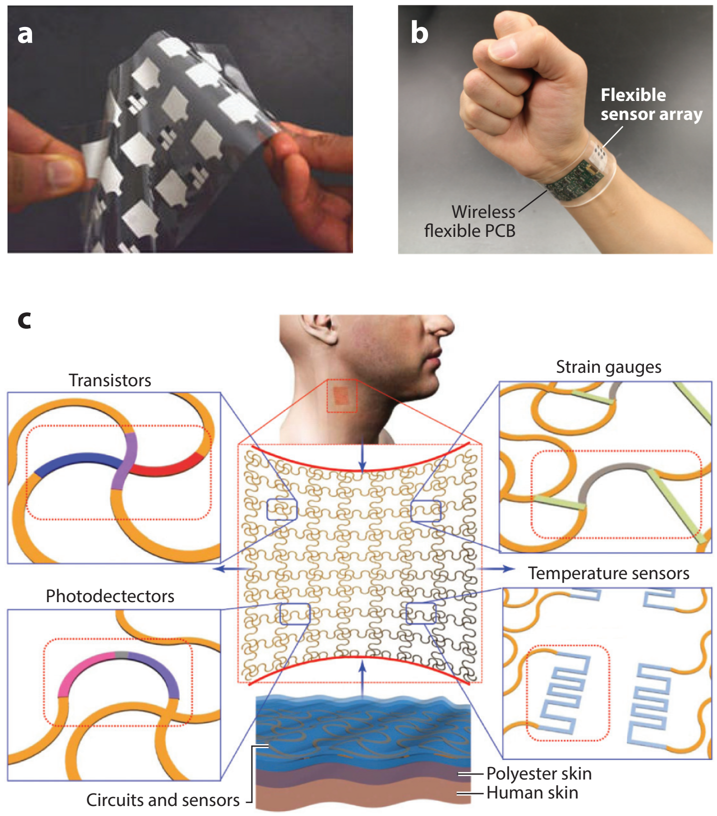

Figure 3

Examples of wearable sensors: (*a*) Skin-worn wearable for real-time monitoring of lactate and electrocardiogram using electrochemical sensor and bipolar electrodes. Adapted with permission from Reference 133. Copyright 2016, Springer Nature. (*b*) Smart wristband for multiplexed perspiration analysis. Adapted with permission from Reference 86. Copyright 2016, Nature Publishing Group. (*c*) Flexible skin. Adapted with permission from Reference 134. Copyright 2011, AAAS.

Recon Jet (Recon Instruments; Vancouver, BC), and JINS MEME (Jin-Co Ltd., Japan) are some examples of wearable glasses. The video and audio capturing abilities of smart glasses can be used to record and archive educational videos for biomedical experts: for example, how to perform surgical operations (64) or in general for training and educating new professionals. Moreover, smart glasses can be used to monitor physiological parameters such as heart rate and respiratory rate (32) and as a rapid diagnostic test reader for quantifying the intensity levels of a test line for different target analyte concentrations (65). As another example, a wearable glass platform for healthcare providers, introduced by Evena Medical (Roseville, CA), provides clinicians with an easy means of finding patients' veins using infrared sensors (62).

Smart contact lenses are contact lenses embedded with multisensors (e.g., pressure and temperature sensors). They are similar to implants but do not require any surgical operation and can be easily worn or removed by the user. Possible biomedical uses of smart lenses include detecting the glucose levels in tears, improving vision without glasses by focusing the eye instantly (66), and monitoring the progression of glaucoma in patients by constantly measuring the curvature of the eye lens (67).

Hats, helmets, and headbands can be also embedded with wearable sensors. The smart hat and smart headband introduced by Spree Wearables, Inc. (Dallas, TX) and the LifeBEAM Helmet monitor the parameters commonly tracked by other wearables, such as heart rate and body temperature, using a built-in advanced plethysmograph, as well as optical and other sensors (68, 69). Other than activity monitoring, wearables worn on the head can be used to measure brain activity. For example, SmartCap, introduced by SmartCap Technologies (Australia) (70) is a fatigue monitoring system that measures brainwave signals for the risk of microsleep, which is an unintended/uncontrolled sleep for a duration of 5–10 s. The Melon headband (71) and IMEC electroencephalographic (EEG) headset (72) monitor the brain's EEG signals to measure mental activity for clinical and research applications, such as for the estimation or quantification of a user's focus levels.

Wearables worn on the ear include hearing aids, earbuds, earrings, and earphones that monitor physiological parameters using pulse oximetry (15, 16, 20). The X-Patch (X2 Biosystems Inc.; Redwood City, CA) is another wearable device worn on the back side of the ear that monitors potential head injuries, which are important for people taking part in sporting activities, and for military personnel and industrial workers (73).

Certain wearables are worn inside the mouth. Examples include a mouthguard for detecting different levels of uric acid or lactate in the saliva (74) and DentiTrac, which is an oral device worn on any oral appliance and used to monitor sleep apnea and adherence of patients to sleep therapy (35).

3.2. Torso

The torso is the central part of the body in which most of the organs are housed. Suits, belts, and underwear are some examples of wearable technologies worn on the torso.

Some examples of wearable technologies worn as a suit include pajamas for electrocardiogram measurement in babies (75), baby glove swaddles for temperature sensing (76), smart jackets for monitoring the physiological parameters of newborn infants (77), military uniforms with a wearable computer to continuously monitor military personnel and protect them, e.g., from environmental threats (78), and swimsuits with a UV sensor (79).

Patches or tattoos with wireless connectivity also hold great promise for the continuous monitoring of vital parameters and improving patient health. The compatibility of patches with several key applications have been demonstrated, such as a tattoo for measuring the skin temperature of a baby (29), a plaster for sweat analysis (6), and patches for drug delivery (80), pain relief (58), and repelling mosquitoes (54).

Smart fabrics, which are textiles embedded with electronics, are also types of wearable sensors worn on the torso. A few examples include the smart bra (81) and shirts for monitoring physiological parameters such as heart rate and respiration rate (26, 82, 83), as well as the chest belt as a sensor for monitoring the respiration rate (31).

Artificial organs (43, 57) are also available as wearable systems. A good example is the wearable pancreas, Genesis, introduced by Pancreum, Inc. (San Francisco, CA). It is used for measuring and regulating glucose levels in the blood together with a smartphone application (43).

3.3. Arm, Leg, and Foot

Wearable devices worn on the arm, leg, and foot are mostly accessories such as smart watches (17, 21), bracelets (52), rings (25, 84), armbands (85), and wristbands (22–24) that can monitor physiological parameters such as body temperature and heart rate (86), UV exposure levels (87), and daily activities. Smart socks (88) and sleeves for injury prevention (89) are a few of the wearable accessories worn on the foot or leg. Smart socks, introduced by Alpha-Fit GmbH (Wertheim, Germany), provide 3D dynamic measurement of pressure distribution over the entire foot while a patient is walking. This foot pressure distribution serves as valuable data for orthopedic shoemakers in fabricating custom shoes for diabetic foot syndrome.

3.4. Ingestible and Implantable Wearables

Ingestible pills, introduced by Proteus Digital Health (Redwood City, CA), are smart pills for monitoring the precise time at which medicine is taken. When the smart pill reaches the stomach, it is powered up with the chemical reaction with the stomach fluid and sends an ingestion time signal to the patch worn on the body. This patch not only communicates with the smart pill but also monitors heart rate, blood pressure, pH, and temperature (90, 91).

Another example of implantable wearables is a pacemaker that is used to treat irregular heartbeats, known as arrhythmias. Once it detects an irregular heartbeat, it provides low-energy electrical pulses to restore the normal rhythm. The ICD is a newer version of a pacemaker, which operates in the same manner. However, if the heartbeat cannot be restored to a normal rhythm, the ICD provides high-energy electrical pulses (92).

Another recent example of implantable wearables is a pulse generator, which is used for deep brain stimulation (93). It is a battery-operated device with a similar size to a stopwatch. It is implanted in the brain by means of surgery and provides electrical signals to control movement, particularly for patients with Parkinson's disease.

4. MATERIALS USED IN FABRICATION OF WEARABLES

Wearables are worn mostly on the soft and curved parts of the human body and require flexible electrodes or sensors to continuously measure physiological parameters without losing the precision and accuracy of the data obtained during their use.

Smart textiles and stretchable electronics are two emerging material technology fields that offer considerable promise for fabricating thin, flexible, washable, soft, and durable electronics for the next generation of wearables. We focus on these technologies in the following subsections.

4.1. Smart Textiles

Rapid advancements in material technology have enabled the fabrication of electronics that are embedded into fabrics or cloth, resulting in various biomedical applications. One example is biometric shirts, which can be used by civilians or military personnel for a variety of purposes such as environmental sensing (78) and monitoring of physiological parameters (6). The integration of electronics with textiles can be carried out in two ways: (*a*) embedding them into cloth and (*b*) integrating them into the textile fibers, which are flexible and thin materials with a large height-to-length ratio (94). The former method requires textile fibers made of electrically conductive materials, obtained by embedding or twisting conductive powders, particles, fillers, or yarns [e.g., silver (95), copper (96) or carbon (97)] into nonconductive fabric fibers (e.g., Kevlar), or using inherently conductive polymeric fibers [e.g., polyaniline and polpyrrole (94, 98, 99)]. The substrate of the conductive fiber, which is the nonconductive part of the material, provides the desired strength or flexibility, while the embedded conducting elements behave as electrodes on the fabric or yarn. These two parts of the fiber exhibit different physical properties. For example, the resistance of a natural fiber such as wool is affected by air humidity, whereas the electrical resistance of a metal fiber changes with temperature (100). Although the substrate provides strength and flexibility, any damage to the conductive fibers can lead to the loss of electronic functionality, which

Review in Advance first posted on February 28, 2018. (Changes may still occur before final publication.)

is an important property for sensing applications. However, these types of failures can be avoided using a large number of fibers on the surface area (94). Another method of embedding electronics into textiles, which is compatible with batch processing, is the encapsulation of the electronics into a bundle of fibers (101). Using this method, the chip is protected from chemical, mechanical, and thermal stresses and deformations (e.g., day-to-day wearing of the textile-based material) by impregnating a polymer resin between the fiber bundle and electronics. The polymer resin acts like a shield to protect the chip from external effects (such as liquid). Radio frequency identification chips, LEDs, and thermistors are examples of electronic products that can be embedded into yarns.

Smart textiles are used for monitoring the physiological signals of the human body or to control devices wirelessly using interfaces (75, 95, 102). The Adidas miCoach seamless sports bra and racer tank are made of conductive fibers that are knitted into the textile to sense heart pulses (81). The electronic functionality of the wearable sensor is achieved with a module attached to the bra, by means of which the gathered data are transmitted to the receiver, such as a smartphone or smart watch (101). Another commercially available wearable that uses smart textiles is the crewneck smart shirt known as PoloTech, by Ralph Lauren. This machine-washable shirt is made of a fabric composed of 70% polyester, 21% nylon, and 9% spandex, embedded with silver fibers and integrated with a 3D accelerometer. The data collected using the silver fibers are transmitted to an iPhone or iPod via Bluetooth using a USB-charged black box attached to the shirt with five pins; it also monitors heart rate and other daily activities (26). Furthermore, smart textiles have also been used for pressure-sensing applications (95). For example, the smart sock, briefly introduced earlier, is a wearable sensor that provides data regarding the foot structure of patients for the production of custom-fit shoes (88). These orthopedic shoes help patients with diabetic foot syndrome by reducing foot pain and the risk of developing foot ulcers (103).

Smart textiles, in the field of wearable computers or sensors, offer various advantages, including flexibility and multifunctionality. However, several design difficulties still need to be addressed to ensure continuity of their functionalities for selected applications in terms of reliability and stability. Comfort, cost-effectiveness, selection of the sensor positions for different body sizes, the batch production complexity of the integration of electronics into textiles, reusability of smart textile products, and energy consumption are some of the most important issues in these materials that need more research and development (6).

4.2. Stretchable Electronics

The materials used in the design of wearable devices should be flexible, lightweight, thin, and conformable to effectively facilitate personal health monitoring (104). To this end, stretchable electronics present opportunities for bending and stretching of electronic circuits and sensors together with their surroundings. In this field of research, various materials (e.g., paper, leather, and plastic films, particularly polymers) have been used as a substrate to keep the circuit together while achieving the required flexibility (105). Polyethylene terephthalate, polyimide (Kapton), polycarbonate, polyethylene naphthalate, CYTOP, poly(methyl methacrylate), polystyrene, and polydimethylsiloxane (PDMS) are polymers commonly used as a protective dielectric layer for wearable patches (4, 5, 106, 107). Among these, PDMS is mostly used as a dielectric support material owing to its ease of preparation, transparency, stiffness, and biocompatibility. Although PDMS is an effective material for rapid prototyping (105, 106), it results in adhesion problems on nonpolymeric substrates, such as metal surfaces, and requires surface treatments (e.g., oxide coating or ozone treatment) to facilitate the adhesion of PDMS to other surfaces. There are certain other drawbacks to using polymers in wearable technology. For example, they are not suitable for processing steps requiring high temperatures, such as above 300°C, and their mechanical

Review in Advance first posted on February 28, 2018. (Changes may still occur before final publication.)

properties change when they are exposed to temperature and humidity. Moreover, plastic films may allow gas (such as oxygen or water vapor) diffusion through the thickness of the sheets, resulting in changes in the chemical structure of the electrodes, such as oxidation of the metal layers. If there is no need for transparent materials, these drawbacks can be eliminated by using other materials such as thin metal layers as a substrate, which can be processed at high temperatures and do not allow the permeation of oxygen and water vapor (108).

In addition to the substrate, electrodes should also be flexible because the compatibility of electronic circuits with these flexible substrates is important for fully functional devices following long-term use. Various materials can be used to fabricate stretchable electrodes (109), such as conductive inks (110), graphene sheets (111), nanowires (112), nanoribbons (104), and nanotube films (113) with different design structures, including lines (e.g., Peano), loops (e.g., Moore), and branch-like meshes [e.g., filamentary serpentine (106) and Greek cross]. Each of these has a different stress-strain response that can be readily applicable to wearable sensors (**Figure 3**) (114). The sensor-containing stretchable electronics should be in close contact with the body because low impedance between the body and the electrode surface is important for improving the performance of the medical device and providing a high signal-to-noise ratio.

Stretchable electronics have been used in wearable patches, particularly for skin-mounted sensors or electrodes that need to follow the human body shape to monitor physiological parameters in the heart, brain, and muscles (106). For example, Blue Spark Technologies introduced a patch thermometer for measuring the skin temperature of a child (115). This wearable sensor contains a printed flexible battery, continuously senses the temperature, and sends the data to a mobile phone by means of a smart application.

5. STANDARDS IN WEARABLE DEVICES

5.1. Wireless Medical Devices

Wearables are generally used to monitor at least one physiological sign and perform at least one function based on wireless radio frequency communication, such as transferring collected patient data to a source by means of a mobile application (116). There are several advantages to using wireless technology in wearable computers or sensors, including compactness, mobility, allowing doctors remote access to patient data, and providing real-time monitoring of patient data. Although wearable sensor developers in the industry refer to particular standards and guidelines that are specific to their devices, there are several other FDA-recognized standards that exist for wireless medical devices that should be taken into consideration during the design, testing, and use of these wearable devices. The International Organization of Standardization (ISO) (117), International Electrotechnical Commission (IEC) (118), Institute of Electrical and Electronics Engineers (IEEE) (119), American National Standards Institute (ANSI) (120), and Association for the Advancement of Medical Instrumentation (AAMI) (121) are other major organizations that provide such standards.

During the design of medical devices, consideration should be given to the selection of wireless technology, e.g., wireless medical telemetry service, IEEE 802.11 or Bluetooth, wireless connection quality, wireless security, and operation frequency with minimum interference in the operation band of other nearby radio frequency devices, not only in the country in which the product is designed, but also in other countries where it will be used. Failure causes and the associated risks and performance of the technology should be evaluated under low wireless connectivity using certain parameters, such as signal-to-noise ratio, to prevent any loss during data transfer and storage. Because wireless medical devices are associated with radio frequency technology, the properties of the intended use of the medical devices should match the expected performance of the wireless technology. Therefore, it is crucial to consider the functions that will operate wirelessly. For this purpose, ISO 14971, a standard for the estimation, identification, control, and monitoring of risks associated with medical devices, has been used to assess the performance of the devices during the product life cycle (122).

Various devices operate at low-frequency bands (<450 MHz), such as television and metal detectors, and high-frequency bands (450–3,000 MHz), such as cellular phones, whereas most medical devices operate at frequencies ∼2,400 MHz (122). In recent years, there has been a tremendous increase in the number of wireless device users, and with developing technology, the size of these devices has been reduced considerably, so that patients may carry these wireless consumer devices near an implanted medical device while being close to its operating frequency. As a result, the electromagnetic fields that wireless medical devices are exposed to are not the same as prior to 20 years ago. Therefore, it is essential to create an electromagnetically compatible medical device to minimize interference with other devices in complex electric and magnetic fields. ISO 14117 (2012) is a standard that specifies procedures (such as test setup details, test procedure, and performance criteria) for assessing the electromagnetic compatibility of active implantable medical devices used for heart rate irregularity therapies, such as pacemakers and ICDs (123). This standard also provides measures for protecting medical devices from external static or AC magnetic fields faced during usage. The devices that comply with the rules of this standard are designed to have certain specifications, such as device size, sensing limits, and battery life. Within the scope of the standard, the devices are tested for frequency limits of up to 3,000 MHz.

IEC 60601-1-2 is another FDA-recognized technical standard that specifies tests and requirements for the electromagnetic compatibility of wireless medical devices. Two national standards on the electromagnetic compatibility of wireless medical devices are available in the United States: AAMI TIR18 (124) and ANSI C63.18 (125). AAMI TIR18, provided by the US Association for the Advancement of Medical Instrumentation, is a report that specifies recommendations regarding the use of wireless medical devices in healthcare associations, including identification of all radio frequency sources and managing electromagnetic fields to ensure the safety of patients (126). This report also provides very specific guidance on the management of electromagnetic fields and specifies recommendations for the use of wireless medical devices, not only at existing healthcare units, but also for new facilities. These guidelines are for design considerations as well as the placement and shielding of electromagnetic devices to minimize patients' field exposure (127). ANSI C63.18, on the other hand, provides a test methodology for clinical and biomedical engineers to estimate the radiation immunity of medical devices to portable radio frequency transmitters (128).

ISO/IEEE 11073 is a family of standards for medical devices and has a subgroup for personal health devices (PHDs) (129). These PHD standards are based on device specialization and are available for such devices as blood pressure monitors, pulse oximeters, glucose meters, thermometers, weighing scales, and cardiovascular fitness and activity monitors, among others. These standards are based on the operation of two autonomously communicating systems: agents as small inexpensive devices such as a wearable necklace and managers in the form of computational devices such as smartphones. The manager can control the agent and send certain tasks to it, while the agent transfers the collected data to the manager for data processing. The analysis is then shown to the user and/or remotely sent to the healthcare provider (129, 130).

5.2. Mobile Applications

The FDA defines a mobile application as "a software application that can be executed (run) on a mobile platform (i.e., a handheld commercial off-the-shelf computing platform, with or without wireless connectivity), or a web-based software application that is tailored to a mobile platform but is executed on a server" (131). If a mobile application is used as an attachment to a regulated medical device or transforms a mobile device such as a smartphone or tablet into a regulated medical device, it is referred to as a mobile medical application. The FDA regulates mobile applications using a risk-based classification approach, where each classification has different requirements, such as premarket approval. A mobile medical application falls under the regulatory oversight of the FDA because it may present risks to the health of users (131). On the other hand, a regular mobile application is not a medical device and therefore does not fall under the regulatory oversight of the FDA, as it does not constitute risks to the health of users, for example, if it is developed and intended to be used by clinicians as an educational tool (132). Another classification also exists for mobile applications, for which the FDA "intends to exercise enforcement discretion." This is because such applications pose a low risk to the health of users, for example, if the application is for carrying out simple calculations commonly used by healthcare providers, such as body mass index calculation.

6. TECHNICAL CHALLENGES AND FUTURE OUTLOOK

Certain technical challenges still need to be addressed for wide-scale use and deployment of wearables as part of the digital health era. One such challenge is their privacy and security. Wearables are physically small and can store a large amount of data; therefore, it is highly likely that the device and data stored may be lost or even hacked. Development of more secure and encrypted wearables, potentially with tracking capabilities, is desired to reduce privacy and security risks.

Another technical challenge is the personal calibration of wearable devices. Every person is uniquely different, and various factors affect personal health (e.g., family medical history, genetics, and diet); therefore, the symptoms for early disease diagnosis may differ for every person. Thus, personal calibration of devices and machine learning–based analysis of data that are tailored for individuals are required for more accurate and relevant monitoring of the health status of the patient using wearables. Big data approaches driven by large populations (e.g., specific to different countries, races, etc.) are extremely powerful but can be misleading for individuals, and therefore wearable technologies should be aware of "small data" created by an individual and be ready to accurately harness and interpret them. Otherwise, big data streams will shadow outliers and statistically create catastrophic events for some individual patients.

A further challenge is the misalignment of wearables, which affects their measurement quality and accuracy. A wearable device should be capable of operating and gathering accurate data even if there is a misalignment between the user and wearable. This demands smarter designs that can tolerate such misalignments, for example, by using computational approaches and guide star–like internal references or self-calibration protocols. This is especially important considering the variations in human physiology and the size or 3D conformation of different organs on which wearables operate.

The durability and robustness of wearables also require further improvement. Wearables should be capable of operating under different conditions, such as in humid or wet environments and warm temperatures. This would allow continuous parameter monitoring without losing performance during such activities as swimming, showering, or sunbathing (depending on the target application). Wearables made of smart textiles and stretchable electronics should be washable and dryable (including the batteries), and the electrodes should not break when bending or folding the device. Another wearable part that requires increased robustness is the battery; this is especially crucial in GPS tracking, which is an essential tool for wearables that consumes a considerable amount of battery power while in use. The development of new materials that have more energy density and efficiently convert solar, thermal, or mechanical power into electricity will aid in the extension of the battery life. Wireless charging of wearables may be another option. Finally, the next-generation wearables will be even smaller than current versions, and as the size decreases, the packaging of sensors should be carried out in an integrated manner so that they do not lose their efficiency in a small area and can offer slim and even lighter-weight wearable designs.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The Ozcan Research Group at UCLA acknowledges the support of the Presidential Early Career Award for Scientists and Engineers (PECASE), the Army Research Office (ARO; grants W911NF-13–1–0419 and W911NF-13–1–0197), the ARO Life Sciences Division, the National Science Foundation (NSF) CBET Division Biophotonics Program, the NSF Emerging Frontiers in Research and Innovation (EFRI) Award, the NSF EAGER Award, NSF INSPIRE Award, NSF Partnerships for Innovation: Building Innovation Capacity (PFI:BIC) Program, Office of Naval Research (ONR), the National Institutes of Health (NIH), the Howard Hughes Medical Institute (HHMI), Vodafone Americas Foundation, the Mary Kay Foundation, Steven and Alexandra Cohen Foundation, and KAUST. This work is based on research performed in a laboratory renovated by the NSF under grant 0963183, which is an award funded under the American Recovery and Reinvestment Act of 2009.

LITERATURE CITED

1. Elenko E, Underwood L, Zoha D. 2015. Defining digital medicine. *Nat. Biotechnol.* 3(5):456–61
2. Jeong JW, Jang YW, Lee I, Shin S, Kim S. 2009. Wearable respiratory rate monitoring using piezo-resistive fabric sensor. *Proc. World Congr. Med. Phys. Biomed. Eng.*, Munich, Ger., pp. 282–84
3. Kreuzer J. 2012. *Sensor for measuring vital parameters in the ear canal*. US Patent No. CA 2875901
4. Kwak MK, Jeong HE, Suh KY. 2011. Rational design and enhanced biocompatibility of a dry adhesive medical skin patch. *Adv. Mater.* 23(34):3949–53
5. Melzer M, Mönch JI, Makarov D, Zabila Y, Bermúdez GSC, Karnaushenko D. 2015. Wearable magnetic field sensors for flexible electronics. *Adv. Mater.* 27(7):1274–80
6. Nayak R, Wang L, Padhye R. 2015. Electronic textiles for military personnel. In *Electronic Textiles: Smart Fabrics and Wearable Technology*, ed. T Dias, pp. 239–56. Cambridge, MA: Woodhead
7. Cima MJ. 2014. Next-generation wearable electronics. *Nat. Biotechnol.* 32:642–43
8. Greenspon AJ, Patel JD, Lau E, Ochoa JA, Frisch DR, et al. 2012. Trends in permanent pacemaker implantation in the United States from 1993 to 2009: increasing complexity of patients and procedures. *J. Am. Coll. Cardiol.* 60(16):1540–45
9. Lyons MK. 2011. Deep brain stimulation: current and future clinical applications. *Mayo Clin. Proc.* 86(7):662–72
10. Patel S, Park H, Bonato P, Chan L, Rodgers M. 2012. A review of wearable sensors and systems with application in rehabilitation. *J. Neuroeng. Rehabil.* 9(1):21
11. ITU (Int. Telecomm. Union). 2016. *2016 ICT facts and figures*. Rep., ICT, Geneva. **https://www.itu.int/en/ITU-D/Statistics/Documents/facts/ICTFactsFigures2016.pdf**
12. Ozcan A. 2014. Mobile phones democratize and cultivate next-generation imaging, diagnostics and measurement tools. *Lab Chip* 17:3187–94

13. Vashist SK, Mudanyali O, Schneidere EM, Zengerle R, Ozcan A. 2014. Cellphone-based devices for bioanalytical sciences. *Anal. Bioanal. Chem.* 406(14):3263–77
14. Chan M, Estève D, Fourniols JY, Escriba C, Campo E. 2012. Smart wearable systems: current status and future challenges. *Artif. Intell. Med.* 56:137–56
15. Biosensive Tech. 2015. *Ear-O-Smart*. **http://earosmart.com/**
16. Bragi. 2015. *Dash Pro*. **https://www.bragi.com/thedashpro/**
17. Wearable Tech. 2018. *Basis Band B1–Health Tracker*. **https://www.wearable-technologies.com/gadgets-of-the-month/12dec-basis**
18. IndieGoGo. 2015. *BitBite*. **https://www.indiegogo.com/projects/bitbite-lose-weight-improve-your-eating-habits#/story**
19. Stahl SE, An H-S, Dinkel DM, Noble JM, Lee J-M. 2016. How accurate are the wrist-based heart rate monitors during walking and running activities? Are they accurate enough? *BMJ Open Sport Exerc. Med.* 2(1):e000106
20. Cosinuss. 2015. *Cosinuss One*. **https://www.cosinuss.com/products/fitness/**
21. Samsung. 2015. *Gear Fit*. **https://www.samsung.com/us/support/owners/product/gear-fit**
22. Wearable Tech. 2018. *Phyode–W/ME Wristband*. **https://www.wearable-technologies.com/store/phyode-w-me-wristband.html**
23. iHealth. 2015. *iHealth Sense*. **http://www.ihealthlabs.com/blood-pressure-monitors/wireless-blood-pressure-wrist-monitor/**
24. Omron. 2015. *3 Series Wrist Blood Pressure Monitor*. **http://omronhealthcare.com/products/3-series-wrist-blood-pressure-monitor-bp629/**
25. Nonin Med. 2015. *Go2 Fingertip Pulse Oximeter*. **http://go2pulseoximeter.com/**
26. Goode L. 2015. *Ralph Lauren's 'smart' shirt is the ultimate preppy tech*. Aug. 20. **https://www.theverge.com/2015/8/20/9178923/ralph-laurens-polotech-smart-shirt-is-the-ultimate-preppy-tech**
27. Terbizan DJ, Dolezal BA, Albano C. 2002. Validity of seven commercially available heart rate monitors. *Meas. Phys. Educ. Exerc. Sci.* 6(4):243–47
28. Lochner CM, Khan Y, Pierre A, Arias AC. 2014. All-organic optoelectronic sensor for pulse oximetry. *Nat. Commun.* 5:5745
29. VivaLnk. 2015. *Fever Scout*. **http://vivalnk.com/feverscout-3/**
30. Al-Khalidi FQ, Saatchi R, Burke D, Elphick H, Tan S. 2011. Respiration rate monitoring methods: a review. *Pediatr. Pulmonol.* 46(6):523–29
31. Spire. 2015. *Spire Health Tag*. **https://www.spire.io/pages/healthtag**
32. Hernande J, Li Y, Rehg JM, Picar R. 2014. *BioGlass: physiological parameter estimation using a head-mounted wearable device*. Presented at EAI Int. Conf. Wireless Mobile Comm. Healthcare (Mobihealth), 4th, Athens, Greece
33. Am. Assoc. Respir. Care. 2015. Current treatments. *YourLungHealth.Org Blog*. **http://www.yourlunghealth.org/lung_disease/sleep_apnea/treatment/index.cfm**
34. Braebon. 2015. *DentiTrac*. **https://www.braebon.com/products/dentitrac/**
35. Bradley DC. 2015. *Method and apparatus for verifying compliance with dental appliance therapy*. US Patent No. 2015169845 (A1)
36. WHO (World Health Org.). 2007. *Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach*. Rep., WHO, Geneva
37. Belza B, Steele BG, Hunziker J, Lakshminaryan S, Holt L, Buchner DM. 2001. Correlates of physical activity in chronic obstructive pulmonary disease. *Nurs. Res.* 50(4):195–202
38. Moy ML, Mentzer SJ, Reilly JJ. 2003. Ambulatory monitoring of cumulative free-living activity. *IEEE Eng. Med. Biol. Mag.* 22(3):89–95
39. Sherrill DM, Moy ML, Reilly JJ, Bonato P. 2005. Using hierarchical clustering methods to classify motor activities of COPD patients from wearable sensor data. *J. Neuroeng. Rehabil.* 2:16
40. Steele BG, Holt L, Belza B, Ferris S, Lakshminaryan S, Buchner DM. 2000. Quantitating physical activity in COPD using a triaxial accelerometer. *Chest* 117(5):1359–67
41. Atallah L, Zhang J, Lo BPL, Shrinkrishna D, Kelly JL, et al. 2010. Validation of an ear worn sensor for activity monitoring in COPD. *Am. J. Respir. Crit. Care Med.* 181:A1211

42. Natl. Inst. Health Res. 2017. *Implantable and wearable medical devices for chronic obstructive pulmonary disease*. Rep., Natl. Inst. Health Res., London. **https://www.nihr.ac.uk/news-and-events/documents/copd_report_2017.pdf**
43. Pancreum. 2015. *Wearable pancreas*. **http://pancreum.com/index.html**
44. WHO (World Health Org.). 2013. *Cardiovascular diseases (CVDs)*. Fact sheet, updated May, 2017, WHO, Geneva. **http://www.who.int/mediacentre/factsheets/fs317/en/**
45. Reiter H, Muehlsteff J, Sipilä A. 2011. *Medical application and clinical validation for reliable and trustworthy physiological monitoring using functional textiles: experience from the HeartCycle and MyHeart project*. Presented at IEEE Eng. Med. Biol. Soc., Boston, MA
46. Gura V, Ronco C, Nalesso F, Brendolan A, Beizai M, et al. 2008. A wearable hemofilter for continuous ambulatory ultrafiltration. *Kidney Int*. 73(4):497–502
47. Wang Q, Zhao H, Chen W, Li N, Wan Y. 2014. Validation of the iHealth BP7 wrist blood pressure monitor for self-measurement, according to the European Society of Hypertension International Protocol revision 2010. *Blood Pressure Monit*. 19(1):54–57
48. Jimison HB, Pavel M, Pavel J, McKanna J. 2004. Home monitoring of computer interactions for the early detection of dementia. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 6:4533–36
49. Wang H, Zheng H, Augusto JC, Martin S, Mulvenna M, et al. 2010. *Monitoring and analysis of sleep pattern for people with early dementia*. Presented at IEEE Int. Conf. Bioinf. Biomed., Hong Kong
50. Mazilu S, Blanke U, Hardegger M, Troster G. 2014. *GaitAssist: a wearable assistant for gait training and rehabilitation in Parkinson's disease*. Presented at IEEE Int. Conf. Pervasive Comput. Comm., Budapest
51. Biessels GJ, Stakenborg S, Brunner E, Brayne C, Scheltens P. 2006. Risk of dementia in diabetes mellitus: a systematic review. *Lancet Neurol.* 5(1):64–74
52. Everon. 2015. *Vega GPS Bracelet*. **https://everon.fi/en/solutions/vega-gps-safety-solution-and-bracelet**
53. Empatica. 2015. *Embrace*. **https://www.empatica.com/**
54. KitePatch. 2018. *Kite Patch*. **http://www.kitepatch.com/kite-patch/**
55. Turner SL, Li N, Guda T, Githure J, Cardé RT, Ray A. 2011. Ultra-prolonged activation of CO_2-sensing neurons disorients mosquitoes. *Nature* 474(7349):87–91
56. Unicef. 2015. *TermoTell*. **http://wearablesforgood.com/finalist-termotell/**
57. Gura V, Beizai M, Ezon C, Polaschegg H-D. 2005. Continuous renal replacement therapy for end-stage renal disease. The wearable artificial kidney (WAK). *Contrib. Nephrol.* 149:325–33
58. Enso. 2015. *Cur*. **http://www.ensorelief.com/**
59. Valedo. 2015. **http://www.valedotherapy.com/**
60. Lumo. 2018. *Lumo Lift*. **https://www.lumobodytech.com/lumo-lift/**
61. WHO (World Health Org.). 2015. *Skin cancers*. **www.who.int/uv/faq/skincancer/en/index1.html**
62. Evena Med. 2015. *Eyes-On Glasses 3.0*. **https://evenamed.com/eyes-on-glasses/**
63. Airo. 2015. *Airo WristBand*. **https://www.airohealth.com/home**
64. Nair AG, Kamal S, Dave TV, Mishra K, Reddy HS, et al. 2015. Surgeon point-of-view recording: using a high-definition head-mounted video camera in the operating room. *Indian J. Ophthalmol.* 63(10):771–74
65. Feng S, Caire R, Cortazar B, Turan M, Wong A, Ozcan A. 2014. Immunochromatographic diagnostic test analysis using Google Glass. *ACS Nano* 8(3):3069–79
66. Google. 2014. Introducing our smart contact lens project. *Google Blog*, Jan. 16. **http://googleblog.blogspot.com.tr/2014/01/introducing-our-smart-contact-lens.html**
67. Columbia Univ. Med. Cent. 2015. *New 'smart' contact lens could improve vision, predict glaucoma risk*. Mar. 14. **http://newsroom.cumc.columbia.edu/blog/headline/new-smart-contact-lens-improve-vision-predict-glaucoma-risk/**
68. Spree Wearables. 2015. *SmartCap*. **http://spreewearables.com/**
69. Lazer. 2015. *LifeBeam*. **http://www.lazersport.com/news/lifebeam-%E2%80%93-heart-rate-monitor-your-helmet**
70. SmartCap Tech. 2015. **www.smartcaptech.com**
71. Dodson B. 2013. Melon Headband aims to measure mental focus. *Health & Wellbeing*, May 21. **https://newatlas.com/melon-headband-eeg-mental-focus/27518/**

Review in Advance first posted on February 28, 2018. (Changes may still occur before final publication.)

72. IMEC. 2015. *Wearable EEG solutions*. **http://www.imec-int.com/drupal/sites/default/files/2017-02/EEG%20HEADSET%202.pdf**
73. X2 Biosyst. 2015. *X2 Ice*. **http://www.x2biosystems.com/**
74. Kim J, Imani S, de Araujo WR, Warchall J, Valdés-Ramírez G, et al. 2015. Wearable salivary uric acid mouthguard biosensor with integrated wireless electronics. *Biosens. Bioelectron.* 74:1061–68
75. Coosemans J, Hermans B, Puers R. 2006. Integrating wireless ECG monitoring in textiles. *Sens. Actuators A* 130–131:48–53
76. Baker CR, Armijo K, Belka S, Benhabib M, Bhargava V, et al. 2007. *Wireless sensor networks for home health care*. Presented at Int. Conf. Adv. Inf. Netw. Appl., 21st, Niagara Falls, Can.
77. Bouwstra S, Chen W, Feijs L, Oetomo SB. 2009. Smart jacket design for neonatal monitoring with wearable sensors. *IEEE Body Sens. Netw.* 40:162–67
78. Berzowska J. 2005. Electronic textiles: wearable computers, reactive fashion, and soft computation. *Text. J. Cloth Cult.* 3(1):58–75
79. Spinali Design. 2016. **https://www.spinali-design.com**
80. Gentag. 2017. *NFC and optical skin patches*. **http://gentag.com/nfc-skin-patches/**
81. Berglin L. 2013. *Smart textiles and wearable technology—a study of smart textiles in fashion and clothing*. Rep. Baltic Fashion Proj., Univ. Borås
82. Kent L, O'Neill B, Davison G, Nevill A, Elborn J, Bradley J. 2009. Validity and reliability of cardiorespiratory measurement recorded by the Lifeshirt during exercise tests. *Respir. Physiol. Neurobiol.* 167(2):162–67
83. Smartex. 2012. *Wearable Wellness System (WWS)*. **http://www.smartex.it/en/our-products/232-wearable-wellness-system-wws**
84. Oura. 2015. *Oura smart ring*. **http://ouraring.com/**
85. Biovotion. 2017. **http://www.biovotion.com/**
86. Gao W, Emaminejad S, Nyein HYY, Challa S, Chen K, et al. 2016. Fully integrated wearable sensor arrays for multiplexed *in situ* perspiration analysis. *Nature* 529(7587):509–14
87. Raymio. 2017. *Your personal suncoach*. **http://raymio.com/**
88. Alphafit. 2015. *Smart sock*. **http://www.alpha-fit.de/en/products/smartsock.html**
89. Munro B, Campbell T, Wallace G, Steele J. 2008. The intelligent knee sleeve: a wearable biofeedback device. *Sens. Actuators B* 131(2):541–47
90. Proteus Digit. Health. 2015. *U.S. FDA accepts first digital medicine new drug application for otsuka and proteus digital health*. Sept. 10. **http://www.proteus.com/press-releases/u-s-fda-accepts-first-digital-medicine-new-drug-application-for-otsuka-and-proteus-digital-health/**
91. Medtronic. 2018. *SmartPill^{TM} Motility Testing System*. **http://www.medtronic.com/covidien/en-us/products/motility-testing/smartpill-motility-testing-system.html**
92. NIH (Natl. Inst. Health). 2017. *What is an implantable cardioverter defibrillator?* NIH, Washington, DC. **http://www.nhlbi.nih.gov/health/health-topics/topics/icd**
93. NIH (Natl. Inst. Health). 2017. *Deep brain stimulation for Parkinson's disease*. NIH, Washington, DC. **https://www.ninds.nih.gov/Disorders/All-Disorders/Deep-Brain-Stimulation-Parkinsons-Disease-Information-Page**
94. Cork CR. 2015. Conductive fibres for electronic textiles: an overview. In *Electronic Textiles: Smart Fabrics and Wearable Technology*, ed. T Dias, pp. 3–20. Cambridge, MA: Woodhead
95. Lee J, Kwon H, Seo J, Shin S, Koo JH, et al. 2015. Conductive fiber-based ultrasensitive textile pressure sensor for wearable electronics. *Adv. Mater.* 27(15):2433–39
96. Perumalraj R, Dasaradan BS. 2010. Electromagnetic shielding effectiveness of doubled copper-cotton yarn woven materials. *Fibres Text. East. Eur.* 80(3):74–80
97. Behabtu N, Young CC, Tsentalovich DE, Kleinerman O, Wang X, et al. 2013. Strong, light, multifunctional fibers of carbon nanotubes with ultrahigh conductivity. *Science* 339(6116):182–86
98. Stoppa M, Chiolerio A. 2014. Wearable electronics and smart textiles: a critical review. *Sensors* 14(7):11957–92
99. Devaux E, Koncar V, Kim B, Campagne C, Roux C, et al. 2007. Processing and characterization of conductive yarns by coating or bulk treatment for smart textile applications. *Trans. Inst. Meas. Control* 29:355–76

100. Yu Y, Zhang J, Liu J. 2013. Biomedical implementation of liquid metal ink as drawable ECG electrode and skin circuit. *PLOS ONE* 8(3):e58771
101. Dias T, Ratnayake A. 2015. Integration of micro-electronics with yarns for smart textiles. In *Electronic Textiles: Smart Fabrics and Wearable Technology*, ed. T Dias, pp. 109–16. Cambridge, MA: Woodhead
102. Löfuede J, Seoane F, Thordstein M. 2010. *Soft textile electrodes for EEG monitoring*. Presented at IEEE Int. Conf. Inf. Tech. Appl. Biomed., 10th, Corfu, Greece
103. Bosowski P, Hoerr M, Mecnika V, Gries T, Jockenhovel S. 2015. Design and manufacture of textile-based sensors. In *Electronic Textiles: Smart Fabrics and Wearable Technology*, pp. 75–107. Cambridge, MA: Woodhead
104. Kim DH, Rogers JA. 2008. Stretchable electronics: materials strategies and devices. *Adv. Mater.* 20(24):4887–92
105. Kim D-H, Kim Y-S, Liu Z, Song J, Kim H-S, et al. 2010. Stretchable silicon electronics and their integration with rubber, plastic, paper, vinyl, leather and fabric substrates. *Mater. Res. Soc. Proc.* 2009:1196-C01–03
106. Kim D-H, Lu N, Ma R, Kim Y-S, Kim R-H, et al. 2011. Epidermal electronics. *Science* 333(6044):838–43
107. Zang Y, Zhang F, Huang D, Gao X, Di C, Zhu D. 2015. Flexible suspended gate organic thin-film transistors for ultra-sensitive pressure detection. *Nat. Commun.* 3(6):6269
108. Hong Y, Chung S, Kattamis A, Cheng I-C, Wagner S. 2007. Technical issues of stainless steel foil substrates for OLED display applications. *Proc. SPIE 6655*, Organ. Light Emitting Mater. Devices XI, 665501
109. Guo CF, Sun T, Liu Q, Suo Z, Ren Z. 2014. Highly stretchable and transparent nanomesh electrodes made by grain boundary lithography. *Nat. Commun.* 5:3121
110. Dupont. 2014. *Printed wearables: electronic inks for the wearable world*. **http://www.dupont.com/content/dam/dupont/products-and-services/electronic-and-electrical-materials/documents/prodlib/DuPont-Electronic-Inks-for-the-Wearable-World.pdf**
111. Kim KS, Zhao Y, Jang H, Lee SY, Kim JM, et al. 2009. Large-scale pattern growth of graphene films for stretchable transparent electrodes. *Nature* 457(7230):706–10
112. Rathmell AR, Bergin SM, Hua YL, Li ZY, Wiley BJ. 2010. The growth mechanism of copper nanowires and their properties in flexible, transparent conducting films. *Adv. Mater.* 22(32):3558–63
113. Hecht DS, Hu L, Irvin G. 2011. Emerging transparent electrodes based on thin films of carbon nanotubes, graphene, and metallic nanostructures. *Adv. Mater.* 23(13):1482–513
114. Fan JA, Yeo W-H, Su Y, Hattori Y, Lee W, et al. 2014. Fractal design concepts for stretchable electronics. *Nat. Commun.* 5:3266
115. Blue Spark Tech. 2017. *TempTraq*. **http://bluesparktechnologies.com/**
116. FDA (US Food Drug Admin.). 2014. *Wireless medical devices*. **https://www.fda.gov/medicaldevices/digitalhealth/wirelessmedicaldevices/default.htm**
117. ISO (Intl. Org. Stand.). 2015. **http://www.iso.org/iso/home.html**
118. IEC (Int. Electrotech. Comm.). 2015. **http://www.iec.ch/**
119. IEEE Stand. Assoc. 2015. **http://standards.ieee.org/**
120. ANSI (Am. Natl. Stand. Inst.). 2015. **http://ansi.org/**
121. AAMI (Assoc. Adv. Med. Instrum.). 2015. **http://www.aami.org/**
122. FDA (US Food Drug Admin.). 2013. *Guidance, compliance & regulatory information (biologics)*. **http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm**
123. ISO (Intl. Org. Stand.). 2012. *ISO 14117:2012. Active implantable devices—electromagnetic compatibility—EMC test protocols for implantable cardiac pacemakers, implantable cardioverter defibrillators and cardiac resynchronization devices.* **https://www.iso.org/standard/54472.html**
124. AAMI (Assoc. Adv. Med. Instrum.). 2010. *AAMI TIR18:2010. Guidance on electromagnetic compatibility of medical devices in healthcare facilities.* Tech. Inf. Rep., AAMI, Arlington, VA. **http://my.aami.org/aamiresources/previewfiles/TIR181003_preview.pdf**
125. ANSI (Am. Natl. Standards Inst.). 2014. *IEEE/ANSI C63.18–2014. American National Standard Recommended practice for an on-site, ad hoc test method for estimating electromagnetic immunity of medical devices to radiated radio-frequency (RF) emissions from RF transmitters.* Rep., Am. Natl. Standards Inst., New York. **https://webstore.ansi.org/RecordDetail.aspx?sku=IEEE%2FANSI+C63.18-2014**

126. AAMI. (Assoc. Adv. Med. Instrum.). 2010. *AAMI TIR18/Ed.2 (2010). Guidance on electromagnetic compatibility of medical devices in healthcare facilities.* **https://infostore.saiglobal.com/en-us/Standards/AAMI-TIR-18-Ed-2-2010–1411361/**
127. Hoolihan D. 1998. Protecting devices from radio frequency transmitters. *Medical Device and Diagnostic Industry Magazine*, Apr. 1. **https://www.mddionline.com/protecting-devices-radio-frequency-transmitters**
128. FDA (US Food Drug Admin.). 2013. *Electromagnetic compatibility—documents available to help resolve medical device EMC problems*. Rep., FDA, Washington, DC. **https://www.fda.gov/Radiation-EmittingProducts/RadiationSafety/ElectromagneticCompatibilityEMC/ucm116592.htm**
129. IEEE Stand. Assoc. 2015. *PHD—Personal Health Device*. **https://standards.ieee.org/develop/wg/PHD.html**
130. Clarke M, Bogia D, Hassing K, Steubesand L, Chan T, Ayyagari D. 2007. *Developing a standard for personal health devices based on 11073*. Presented at IEEE Annu. Int. Conf. Eng. Med. Biol. Soc., 29th, Lyon, France. **http://ieeexplore.ieee.org/stamp/stamp.jsp?arnumber=4353764**
131. FDA (US Food Drug Admin.). 2015. *Mobile medical applications: guidance for industry and FDA staff*. Rep., FDA, Washington, DC. **http://www.fda.gov/downloads/MedicalDevices/.../UCM263366.pdf**
132. Mavandadi S, Dimitrov S, Feng S, Yu F, Sikora U, et al. 2012. Distributed medical image analysis and diagnosis through crowd-sourced games: a malaria case study. *PLOS ONE* 7(5):e37245
133. Imani S, Bandodkar AJ, Mohan AMV, Kumar R, Yu S, et al. 2016. A wearable chemical-electrophysiological hybrid biosensing system for real-time health and fitness monitoring. *Nat. Commun.* 7:11650
134. Ma Z. 2011. An electronic second skin. *Science* 333(6044):830–31
135. Vancive. 2017. **https://vancive.averydennison.com/en/home.html**
136. Noh S, Yoon C, Hyun E, Yoon HN, Chung TJ, et al. 2014. Ferroelectret film-based patch-type sensor for continuous blood pressure monitoring. *Electron. Lett.* 50:143–44