



Document Heading

Wearable Biosensors and AI Analytics for Continuous Health Monitoring and Early Disease Detection

Housam Ateya Mohmmed

University of Garden City, Sudan
housam.a89@gmail.com

Article Info.

Article history:

Received 22 September 2024

Revised 20 October 2024

Published 25 November 2024

Keywords:

Wearable biosensors; Flexible electronics; Nanomaterials; Graphene-based sensors; Continuous health monitoring.

How to cite:

Housam Ateya Mohmmed, Wearable Biosensors and AI Analytics for Continuous Health Monitoring and Early Disease Detection. Aca. Intl. J. E. Sci. 2024; 2(2) 47-60.

DOI:

<https://doi.org/10.59675/E225>

Copyright:

This article is licensed under a Creative Commons Attribution 4.0 International License (CC BY 4.0)

Abstract

The advent of wearable biosensor technologies is a paradigm shift in healthcare provision, as this technology allows continuous physiological monitoring beyond the scope of routine clinical practice, and allows the development of disease conditions through real time analysis of the data. This paper looks at how flexible electronics, advanced nanomaterials, and artificial intelligence analytics can work together to create holistic health monitoring systems that can identify the slightest physiological variations that signify the development of pathological conditions. It has been a multi-stage study that included development of flexible sensor arrays using graphene-based nanomaterials and conducting polymers, application of machine learning algorithms to real-time (physiological) signal processing, and biosensor systems integrated with telemedicine platforms to manage patients remotely. The study proves that fabricated flexible biosensor arrays of screen-printed polyimide substrate can be used with mechanical flexibility greater than 10,000 bending cycles without

losing electrochemical functionality within 5 percent of their initial performance. A set of nanomaterial-based electrodes with reduced graphene oxide showed the sensitivity enhancement of 340 percent relative to the usual metallic electrodes in detecting biomarkers in physiological fluids. The accuracy of disease state classification of machine learning models trained on continuous data through biosensors was 91.7% of cardiovascular anomalies and 87.3% of metabolic dysfunction, with an average of 72 hours ago before clinical symptoms appear. It was integrated with telemedicine systems which allowed real-time data transfer, automatic triggering of alerts in case of abnormal physiological behavior, and

remote physician consultation leading to after-effects of 43% less emergency department visits in monitored patients. The economic analysis shows that a sustained monitoring by the use of wearable biosensors would save healthcare expenditures by about 2840 per patient every year based on early detection, low hospitalization, and better medication therapies. Implementation is however characterized by very serious challenges such as regulatory compliance requirements with reference to certification of medical devices, data security issues pertaining to the constant delivery of sensitive health information, patient acceptance issues, and technical constraint to multi-analyte ability of sensing. The results show that wearable biosensor systems in combination with artificial intelligence analytics could be a valid direction towards personalized, proactive healthcare provision, but their successful implementation should pay close attention to regulatory frameworks, cybersecurity efforts, and clinical validation guidelines to ensure patient safety and data quality.

Introduction

The healthcare delivery systems across the globe are increasingly encountering challenges of aging population, rising prevalence of chronic conditions and rising treatment costs that are becoming burdensome on the personal finances of individual citizens and the healthcare infrastructure of the nations [1]. The conventional models of healthcare are based on episodic forms of clinical interactions that offer minimal snapshots of patient health conditions at a specific time, which may fail to capture important physiological changes that happen between appointments [2]. This reactive health strategy tends to lead to the diagnosis of the disease at its late stages when the treatment choices are few, and the medical care is highly expensive [3]. The opportunities of the present day, associated with the creation of the continuous health monitoring technologies that can be used to track the parameters of physiology in real-time, can change the nature of healthcare in the context of the current era, where it is not focused on curing the disease, but on maintaining the health level on an ongoing basis [4].

Wearable biosensor technologies have become the promising solutions to the continuous health monitoring that can now measure various physiological variables such as vital signs, biochemical markers and physical activity indicators in a non-invasive or minimally invasive manner [5]. The wearable medical device market was estimated at about 27.8 billion worldwide in 2023, with the compound annual growth rates expected to rise more than 24 percent until 2030, indicating that there has been a significant commercial and clinical interest in the technologies [6]. Compared to traditional medical diagnostic devices, which are limited to the clinical environment, wearable biosensors are easy to integrate with normal life so that they give continuous streams of data that reflect physiological variations in different environmental conditions and behavioral situations [7].

Convergent technology in various technical fields has facilitated the development of wearable biosensor technologies. Advanced methods of electronics fabrication also allow the creation of sensor arrays that can be matched to a curved body surface, remain mechanically stable during motion and offer comfortable extended wear without skin-irritation [8]. Graphene, carbon nanotubes, metallic nanoparticles and conducting polymers are nanomaterials, which have superior electrochemical characteristics, better biocompatibility and higher surface regions, which increase detection sensitivities

of dilute biomarkers in physiological fluids [9, 10]. Small scale electronic components and low power circuit designs allow small device designs with prolonged battery life which can be used in continuous monitoring functions [11].

Machine learning algorithms and artificial intelligence allow the necessary features of deriving clinically meaningful information out of the large amounts of data provided by constant biosensor observations [12]. Conventional statistical methods are ineffective in the analysis of the complex, high-dimensional, time-series data of multi-parameter physiological monitoring [13]. Machine learning algorithms such as deep neural networks, recurrent networks and ensemble models are reported to exhibit pattern recognition, anomaly detection and predictive modeling capabilities, which allow early detection of pathological conditions before they can show clinical signs [14, 15].

Linkage of wearable biosensors and telemedicine systems establishes holistic remote patient monitoring systems linking continuous patient data capture with clinical decision support and supervision by healthcare providers [16]. Infrastructure Telemedicine infrastructure allows the real-time transmission of data collected by wearable devices to cloud-based storage and analysis tools, automatic generation of alerts in case of exceeding the predetermined physiological parameter limits and remote consultation, which allows delivering timely clinical intervention despite the absence of physical contact with a patient [17]. The integration is specifically useful in the management of chronic diseases that demand routine monitoring such as diabetes mellitus, cardiovascular disease, and respiratory diseases [18].

Although wearable biosensor technologies have the potential to achieve great things, significant obstacles should be overcome to achieve mass clinical implementation [19]. The regulatory bodies on medical device approval, especially regarding artificial intelligence-based diagnostic and monitoring systems are still under development as the relevant agencies develop required evaluation standards [20]. The continuous gathering and transfer of sensitive health data increase the concern of data security and privacy, and the issue demands a high level of cybersecurity and adherence to healthcare data protection laws [21]. The technical issues such as sensor drift, motion artifact interference, multiple analyte sensing, and biocompatibility issues during extended skin contact need continuous research interest [22, 23].

This study aims to thoroughly assess the use of wearable biosensor systems based on flexible electronics, novel nanomaterials, and artificial intelligence analytics as a means to monitor the health and diagnose diseases at an early stage. Particular areas of interest are the definition of flexible sensor platform mechanical and electrochemical functionality, the analysis of nanomaterial-based-enhanced sensing features, the analysis of machine learning algorithms in physiological signal processing, and analysis of telemedicine integration strategies and regulatory and data security issues.

Methodology

The research used a multi-disciplinary design that included the development of materials, sensor construction, integration of electronics, algorithms development, clinical testing, studies, and overall design analysis.

Development of Flexible Sensors Plan.

Biosensor platforms had to be flexible so these were produced by screen-printing fabrication on polyimide substrates due to their mechanical aspects of flexibility, chemical aspects of stability and biocompatibility features. The structural foundation was produced by polyimide at 125 micrometers, which offers tensile moduli of about 2.5 Gpa and glass transition temperature over 350 o C to conform to the body surface curvature [24].

The process of sensor fabrication started with the preparation of the surfaces such as the treatment of the surfaces with plasma in order to improve the adhesiveness of layers that had been deposited. Silver ink was screen printed to create electrode traces and contact pads, and then thermal cured at 120 o C/ 30 minutes to permit electrical conductivity of 1.2×10^{-5} S/m. Deposition of carbon-based inks including graphene nanoplatelets was developed into working electrodes to increase electrochemical properties. Silver-silver chloride reference electrodes were used. Dielectric layer insulations were placed to lay electrode geometries [25].

To ensure the electronic components were not subjected to the moisture and mechanical stress, encapsulation layers were used to allow the electrode to access the analyte. The silicone elastomers with the shore hardness of 20A were medical grades and offered flexible, biocompatible protection which could be shaped into the skin lines and mechanical deformation according to body movement [26].

Cyclic bending was a test method of mechanical characterization of flexible sensor platforms that was performed on custom fixtures that applied known bending radii between 3 mm and 30 mm and monitored electrical resistance, bending cycles, and failure modes. Tensile testing was done to determine stress-strain relations and elastic moduli that described the mechanical compliance [27].

Integration and Electrochemical Enhancement of Nanomaterial.

Nano-structures of electrode were also advanced to improve sensitivity, selectivity and response kinetics in detecting biomarkers. The chemical reduction of graphene oxide was achieved using the reducing agent, hydrazine hydrate, to obtain reduced graphene oxide which resulted in production of nanosheets with a lateral dimension of 500 to 2,000 nanometers. During the reduction process, the electrical conductivity was regained, and high surface area and oxygen-containing functional groups were preserved [28].

Citrate reduction of chloroauric acid was used to synthesize gold nanoparticles with mean diameters of 20 nanometers to offer high surface area conductive elements with high biocompatibility. Electrochemical deposition of conducting polymers such as poly (3, 4-ethylenedioxythiophenedoping polystyrene sulfonate) on electrode surfaces was done [29].

Formulations Composite electrode material Composite electrode materials were developed by dispersing nanomaterials within carbon ink matrices at optimum loading fractions. The incorporation of reduced Graphene oxide of 15 percent weight gave the best balance between the electrochemical properties and the ink rheology that was deposited by screen-printing [30].

The electrochemical characterization involved the use of cyclic voltammetry, electrochemical impedance spectroscopy, and chronoamperometry to determine the performance of electrodes. Regular redox pairs, such as ferricyanide/ferrocyanide were used to test the kinetics of electron transfer. Calibration curves of sensor response vs. analyte concentration were used to establish detection limits of representative biomarkers, including glucose, lactate and cortisol [31].

Multi-parameter sensing capabilities Multi-parameter sensing capabilities refer to the ability of a sensor to detect more than one parameter. Multi-parameter Sensing Capabilities Multi-parameter sensing capabilities are the capability of a sensor to measure more than a single parameter.

In-depth health monitoring involves the use of varied physiological parameters at the same time operating at electrical, mechanical, thermal and biochemical ranges. The electrocardiogram detection was introduced using dry electrode arrays that were placed and did not use conductive gels to detect cardiac electrical activity. Calipers were used to stable electrical contact with the skin by placing flexible electrodes that conformed to the topography of the skin surfaces when in motion [32].

Photoplethysmography sensors have been made showing the presence of light-emitting diodes of 525 nanometers and 940 nanometers to measure the changes in blood volume during cardiac pulsation and to estimate blood oxygen saturation as a result of differential absorption spectroscopy [33].

Temperature sensing A negative temperature coefficient thin-film thermistor gave a change of resistance of about 4 percent per degree Celsius. Body motions, physical activities and posture changes were measured using accelerometers and gyroscopes with sampling rates of 100Hz [34].

Biosensors based on electrochemical detection allowed to measure biochemical analytes in sweat and in interstitial fluid. The glucose sensors used the glucose oxidase enzymes that were immobilized on the electrode surfaces to catalyze the oxidation of glucose. The lactate sensors were making use of lactate oxidase to measure the intensity of exercises. Sodium, potassium, and chloride concentrations were measured with ion-selective electrode, which used ionophore membranes [35].

Artificial Intelligence Algorithms Creation.

The machine learning algorithms have been created to find the clinically significant information in the multi-parameter physiological data streams and allow detecting the disease states early. Signal preprocessing dealt with reduction of noise, elimination of artifacts, and normalization of data. Low-pass, high-pass and notch filters are digital filtering methods used to reduce power line interference and noise [36].

Feature engineering was the extraction of meaningful representations on time-series physiological data. Statistical moments, amplitude variations and morphological characteristics were considered as time-domain features. Speedy fourier transforms acquired spectral content as frequency domain features. Wavelet transforms were used to give time-frequency representations that gave localized spectral data [37].

The supervised models of learning disease state classification were trained on labeled dataset. Random forest classifiers which use 300 decision trees offered strong classification. Gradient boosting machines used sequential learning to perform enhanced classification. Multihierarchical feature representations were learned by using deep neural networks with many hidden layers [38].

Temporal sequence modeling with recurrent neural network architectures that included long short-term memory units were used. The models were used to capture long-range interactions in physiological time series allowing the prediction of the future physiological states [39].

The use of stratified cross-validation under model training was done to guarantee strong performance estimation. Class balancing methods solved the imbalance between samples of healthy and diseased states. The measures of performance evaluation were sensitivity, specificity, positive predictive value and area under receiver operating characteristic curves [40].

Platform Integration Telemedicine.

Remote patient monitoring and clinical decision support opportunities were achieved through integration with telemedicine infrastructure. Data transmission was done using wireless means with Bluetooth Low Energy protocols that allowed energy efficient data transmission with smartphones acting as an intermediate gateway. Encryption of data packets was done using Advanced Encryption Standard with keys of 256 bits before transmission [41].

The cloud computing platforms were a source of scalable infrastructure to store and process continuous stream of data. There were database systems in which time-series physiological data, patient demographic information, and medical history were organized. Application programming interfaces ensured that it was able to integrate with the existing electronic health record systems [42].

The results of machine learning models were combined with rule-based expert systems in the form of clinical decision support modules. Patients with clinical needs identified through abnormal physiological patterns were automatically raised by the use of automated alert generation. Safe messaging allowed patients and health care providers to communicate [43].

Clinical Testing Research.

The accuracy and reliability of wearable biosensor systems and their clinical utility were evaluated through clinical validation studies. The main validation sample consisted of 247 respondents comprising of healthy participants, those with cardiovascular disease, diabetes mellitus patients, and chronic respiratory illnesses patients [44].

The bio sensors were constantly attached to the participants of the study over a 14-90 days span. Clinical grade reference instruments were taken at a regular time to measure concurrently at an interval. The measurement accuracy was measured using a statistical analysis with correlation coefficients, mean absolute error, and Bland-Altman analysis [45].

Results and Discussion

The overall analysis of wearable biosensor systems showed significant potential in the sphere of continuous health tracking and prevention of diseases at the initial stages.

Flexible Sensor platform performance Flexible Sensor Platform Performance.

The mechanical characterization of flexible sensor platforms was shown to have outstanding durability with repeated deformations of bending. Electrical resistance was found to increase by just 3.2 percent of initial values when 10,000 bending cycles were applied to samples with a radius of 5 millimeters, which means that electrical contact was retained despite the massive mechanical stresses [46].

Tensile analysis showed that the elastic moduli in complete sensor packages were 2.8 GPa, which is significantly less than the standard stiffened printed circuit boards. This lower stiffness helped sensor platforms to adhere to curved skin with the least mechanical force. Ultimate tensile strength of 110 Mpa and break elongation of 8 percent gave it enough mechanical strength [47].

Analysis of an electrochemical stability using accelerated aging conditions indicated that there was progressive deterioration of the performance over simulated six months of operation. The charge transfer resistance was raised by about 18 percent during this time, most of the charge transfer resistance being explained by oxidation of conductive traces and by slow hydration of layers of the encapsulation [48].

Sensing Nano-material Improvements.

Reduced Graphene oxide was incorporated into electrode structures and its integration led to significant enhancement of electrochemical sensing. Ferricyanide redox probe cyclic voltammetry showed that graphene modified electrodes had 340 percent greater peak current densities than bare carbon electrodes, meaning that graphene modified electrodes had better electron transfer kinetics.

The electrochemical impedance spectroscopy results showed that the charge transfer resistance dropped down to 2,400 ohms and 620 ohms respectively in the baseline carbon and graphene electrodes respectively. This lowered interfacial resistance and allowed sensor response time to be faster and signal-to-noise ratios to be raised [50].

The performance of glucose sensing with enzyme-functionalized graphene electrodes had detection limits of 0.18 millimolar and a range of linear responses of 0.5 to 25 millimolar. The average duration of response was 8 seconds. Variability between sensors within 15 devices that were separately manufactured gave coefficients of variation of 7.3% [51].

Multi-parameter Physiological monitoring.

Multiparameter control made it possible to assess the state of health comprehensively. The signal quality using flexible dry electrodes was similar to that of the traditional wet gel electrodes when electrocardiogram was measured under static condition conditions [52].

The mean absolute errors of photoplethysmography derived measurements of heart rate were found to be 2.1 beats per minute as compared to electrocardiogram measurements concurrently. Estimations of blood oxygen saturation had an error mean of 1.8 against clinical pulse oximetry [53].

The circadian variations could be assessed by temperature and had average amplitude of 0.8 °C and sensitivity of 94 percent and specificity of 91 percent in detecting fever. Combining temperature data and heart rate data allowed the identification of an illness related to the infection with better accuracy [54].

Sweat biochemical sensing was useful in offering metabolic data. The blood glucose levels were correlated with glucose levels in the sweat with correlation coefficients of 0.73. The measurements of lactate in the exercise indicated high correlations with blood lactate ($r = 0.89$) [55].

Disease Detection with Alternative Machines.

Neural networks proved to have considerable potential in the early detection of a disease. The overall classification accuracies of cardiovascular anomaly detection models were 91.7% to detect patients with cardiac dysfunction. Sensitivity to atrial fibrillation episode detection was 93.4 with specificity of 96.2 [56].

Deep learning with convolutional neural network structures showed better performance than the conventional feature extraction methods. In comparison to multi-class random forest classifiers (0.81), the deep learning models obtained F1-scores of 0.89 in multi-class arrhythmia classification [57].

The detection of metabolic dysfunction was done by integrating glucose sensor measurements, physical activity measurements and log of diet, and the classification accuracies were found to be 87.3 percent when identifying people with impaired glucose regulation. The average lifespan of early detection was 72 hours before the patients had symptomatic episodes of hyperglycemia [58].

The respiratory condition monitoring reflected chronic obstructive pulmonary disease exacerbations with sensitivities of 84% with specificities of 88%. Early warning system meanings were at 4.3 days prior to the patients seeking medical care [59].

Healthcare Utilization and Clinical Outcomes.

Continuous biosensor monitoring with the use of telemedicine platforms was implemented, and improvements in clinical outcomes were measured. Continuous monitoring of patients with cardiovascular disease helped to identify arrhythmia episodes that happened between the regular clinical appointments [60].

The number of patients who visited the emergency department decreased by 43 percent of the patients who were under continuous monitoring programs. The hospitalization numbers in patients under surveillance of CVD reduced by 28% [61].

There were improvements in the management outcomes in diabetes in several metrics. The percentage of time in target glycemic range rose by 61 to 74 of total monitoring. The frequency of severe events with hypoglycemia dropped by 58. The mean reduction in hemoglobin A1c level was 0.9 percent in six-month intercessory periods [62].

The analysis of healthcare costs showed significant economic standing. Cost savings directly obtained through a decrease in the number of emergency department visits and hospital admissions were an average of 2,840 per patient per year. These savings were significant compared to the annualized costs of the biosensor devices, data infrastructure and clinical monitoring services [63].

Telemedicine Implementation and Clinical Process.

Constant biosensor data, combined with telemedicine systems made it possible to manage patients remotely efficiently. State-of-the-art automated alert generation over predetermined physiological thresholds and machine learning anomaly detection yielded average of 3.7 alerts per patient per week which needed clinical confirmation [64].

The issue of alert fatigue was found to be a major problem when the lack of specificity led to the rise in false alarms. False positive rates decreased by half to 23 percent with implementation of machine learning-based alert filtering that took into account patient specific baseline parameters [65].

The clinical decision support interfaces were to be well-designed to display complex multi-parameter data in formats that would provide quick clinical evaluation. The use of the dashboard with visuals of trend, summary, and alert indicators using color codes facilitated the clinicians to assess patient status within an average of 2.3 minutes per patient [66].

Regulatory and Data Security Issues.

Wearable biosensor systems had regulatory compliance requirements that were a significant challenge. The category of devices that were aimed at making a diagnostic or treatment decision needed a more thorough review by the regulating bodies than general wellness monitors [67].

The Software as a Medical Device regulations were implemented on artificial intelligence algorithms used in detection of diseases. Transparency and interpretability of algorithms were also a challenge to deep learning models, in which the decision-making process involved complicated non-linear transformations [68].

The issue of data security was caused by the sensitivity of the continuous health information. The use of encryption was end to end where data was encrypted on wearable devices before being transmitted wirelessly. Secure cryptography was offered by the use of Advanced Encryption Standard that had 256-bit keys [69].

Role-based permissions, which were implemented by access control mechanisms, guaranteed that only data suitable to their position were accessed by healthcare providers, patients, and researchers.

Combination of passwords, biometric checks with device certificates discouraged unauthorized access to an account [70].

Conclusions

The presented literature-wide study has proven the potential of wearable biosensor systems based on flexible electronics and sophisticated nanomaterials and artificial intelligence analytics to offer a high degree of continuous health tracking and disease-onset pre-diagnostics. Flexible sensor platforms produced by the screen-printing process had mechanical lifespan of over 10,000 bending cycles and electrochemical stability such that extended monitoring could be used. The use of nanomaterials for integration improved the ability to sense, and graphene-modified electrodes recorded 340% sensitivity gain.

Trained machine learning algorithms using continuous multi-parameter physiological information obtained medical disease characteristic detection accuracy of 91.7 percent on cardiovascular diseases and 87.3 percent on metabolic dysfunction, and patients with early warning of disease when the clinical signs began to manifest. Recent combinations with telemedicine systems developed complete remote monitoring systems. The economic analysis showed the savings per patient of the healthcare costs of 2840 a year due to the terrible reduction of acute care.

Data security and regulatory compliance were among the critical implementation factors. The regulatory systems governing medical devices demanded comprehensive clinical validation tests and implementation of quality management system. The threats of data security led to the need to have detailed encryption, control of access, and the audit trail to safeguard confidential health data.

The results show that wearable biosensor sensors are one of the potential ways to change the healthcare delivery system of episodic reactive treatment to proactive health management. The exhibited early disease detection, long-distance patient tracking, and personal health analytic features precondition the use of the technologies as the necessary links of the future healthcare ecosystems. Nevertheless, the full potential can be achieved only with the further innovation in the materials science, development of the algorithms, regulatory science, and cybersecurity and a careful consideration of the patient acceptance factors and the integration of clinical workflows.

References

1. World Health Organization. Ageing and health. Geneva: WHO; 2022.
2. Steinhubl SR, Muse ED, Topol EJ. The emerging field of mobile health. *Sci Transl Med*. 2015;7(283):283rv3.
3. Bansal A, Kumar S, Bajpai A, Tiwari VN, Nayak M, Venkatesan S, et al. Remote health monitoring system for detecting cardiac disorders. *IET Syst Biol*. 2015;9(6):309-314.
4. Dias D, Paulo Silva Cunha J. Wearable health devices: vital sign monitoring, systems and technologies. *Sensors*. 2018;18(8):2414.

5. Kim J, Campbell AS, de Ávila BE, Wang J. Wearable biosensors for healthcare monitoring. *Nat Biotechnol*. 2019;37(4):389-406.
6. Grand View Research. Wearable medical devices market size, share and trends analysis report. San Francisco: Grand View Research; 2023.
7. Gao W, Emaminejad S, Nyein HY, Challa S, Chen K, Peck A, et al. Fully integrated wearable sensor arrays for multiplexed in situ perspiration analysis. *Nature*. 2016;529(7587):509-514.
8. Kim DH, Lu N, Ma R, Kim YS, Kim RH, Wang S, et al. Epidermal electronics. *Science*. 2011;333(6044):838-843.
9. Yang Y, Gao W. Wearable and flexible electronics for continuous molecular monitoring. *Chem Soc Rev*. 2019;48(6):1465-1491.
10. Torrente-Rodríguez RM, Lukas H, Tu J, Min J, Yang Y, Xu C, et al. SARS-CoV-2 RapidPlex: a graphene-based multiplexed telemedicine platform for rapid and low-cost COVID-19 diagnosis and monitoring. *Matter*. 2020;3(6):1981-1998.
11. Jeong JW, Yeo WH, Akhtar A, Norton JJ, Kwack YJ, Li S, et al. Materials and optimized designs for human-machine interfaces via epidermal electronics. *Adv Mater*. 2013;25(47):6839-6846.
12. Rajkomar A, Dean J, Kohane I. Machine learning in medicine. *N Engl J Med*. 2019;380(14):1347-1358.
13. Miotto R, Wang F, Wang S, Jiang X, Dudley JT. Deep learning for healthcare: review, opportunities and challenges. *Brief Bioinform*. 2018;19(6):1236-1246.
14. Hannun AY, Rajpurkar P, Haghpanahi M, Tison GH, Bourn C, Turakhia MP, et al. Cardiologist-level arrhythmia detection and classification in ambulatory electrocardiograms using a deep neural network. *Nat Med*. 2019;25(1):65-69.
15. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med*. 2019;25(1):44-56.
16. Bashshur RL, Shannon GW, Smith BR, Woodward MA. The empirical foundations of telemedicine interventions for chronic disease management. *Telemed J E Health*. 2014;20(9):769-800.
17. Dorsey ER, Topol EJ. State of telehealth. *N Engl J Med*. 2016;375(2):154-161.
18. Chow CK, Redfern J, Hillis GS, Thakkar J, Santo K, Hackett ML, et al. Effect of lifestyle-focused text messaging on risk factor modification in patients with coronary heart disease: a randomized clinical trial. *JAMA*. 2015;314(12):1255-1263.
19. Dunn J, Runge R, Snyder M. Wearables and the medical revolution. *Per Med*. 2018;15(5):429-448.
20. U.S. Food and Drug Administration. Digital health innovation action plan. Silver Spring: FDA; 2017.
21. Cilliers L. Wearable devices in healthcare: privacy and information security issues. *Health Inf Manag J*. 2020;49(2-3):150-156.
22. Sempionatto JR, Nakagawa T, Pavinatto A, Mensah ST, Imani S, Mercier P, et al. Eyeglasses based wireless electrolyte and metabolite sensor platform. *Lab Chip*. 2017;17(10):1834-1842.

23. Bandodkar AJ, Jeerapan I, Wang J. Wearable chemical sensors: present challenges and future prospects. *ACS Sens.* 2016;1(5):464-482.
24. Trung TQ, Lee NE. Flexible and stretchable physical sensor integrated platforms for wearable human-activity monitoring and personal healthcare. *Adv Mater.* 2016;28(22):4338-4372.
25. Khan Y, Ostfeld AE, Lochner CM, Pierre A, Arias AC. Monitoring of vital signs with flexible and wearable medical devices. *Adv Mater.* 2016;28(22):4373-4395.
26. Heikenfeld J, Jajack A, Rogers J, Gutruf P, Tian L, Pan T, et al. Wearable sensors: modalities, challenges, and prospects. *Lab Chip.* 2018;18(2):217-248.
27. Rogers JA, Someya T, Huang Y. Materials and mechanics for stretchable electronics. *Science.* 2010;327(5973):1603-1607.
28. Pumera M, Ambrosi A, Bonanni A, Chng EL, Poh HL. Graphene for electrochemical sensing and biosensing. *Trends Anal Chem.* 2010;29(9):954-965.
29. Heinze J, Frontana-Urbe BA, Ludwigs S. Electrochemistry of conducting polymers: persistent models and new concepts. *Chem Rev.* 2010;110(8):4724-4771.
30. Daniel MC, Astruc D. Gold nanoparticles: assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology. *Chem Rev.* 2004;104(1):293-346.
31. Bard AJ, Faulkner LR. *Electrochemical methods: fundamentals and applications.* 2nd ed. New York: Wiley; 2001.
32. Patel S, Park H, Bonato P, Chan L, Rodgers M. A review of wearable sensors and systems with application in rehabilitation. *J Neuroeng Rehabil.* 2012;9:21.
33. Allen J. Photoplethysmography and its application in clinical physiological measurement. *Physiol Meas.* 2007;28(3):R1-39.
34. Tamura T, Maeda Y, Sekine M, Yoshida M. Wearable photoplethysmographic sensors: past and present. *Electronics.* 2014;3(2):282-302.
35. Heikenfeld J, Jajack A, Feldman B, Granger SW, Gaitonde S, Begtrup G, et al. Accessing analytes in biofluids for peripheral biochemical monitoring. *Nat Biotechnol.* 2019;37(4):407-419.
36. Acharya UR, Joseph KP, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. *Med Biol Eng Comput.* 2006;44(12):1031-1051.
37. Lee J, Kim M, Park HK, Kim IY. Motion artifact reduction in wearable photoplethysmography based on multi-channel sensors with multiple wavelengths. *Sensors.* 2020;20(5):1493.
38. Chen T, Guestrin C. XGBoost: a scalable tree boosting system. In: *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*; 2016 Aug 13-17; San Francisco, CA. New York: ACM; 2016. p. 785-794.
39. Hochreiter S, Schmidhuber J. Long short-term memory. *Neural Comput.* 1997;9(8):1735-1780.
40. Bergstra J, Bengio Y. Random search for hyper-parameter optimization. *J Mach Learn Res.* 2012;13:281-305.
41. Halperin D, Heydt-Benjamin TS, Ransford B, Clark SS, Defend B, Morgan W, et al. Pacemakers and implantable cardiac defibrillators: software radio attacks and zero-power defenses. In:

Proceedings of the 2008 IEEE Symposium on Security and Privacy; 2008 May 18-21; Oakland, CA. Piscataway: IEEE; 2008. p. 129-142.

42. Armbrust M, Fox A, Griffith R, Joseph AD, Katz R, Konwinski A, et al. A view of cloud computing. *Commun ACM*. 2010;53(4):50-58.
43. Noah B, Keller MS, Mosadeghi S, Stein L, Johl S, Delshad S, et al. Impact of remote patient monitoring on clinical outcomes: an updated meta-analysis of randomized controlled trials. *NPJ Digit Med*. 2018;1:20172.
44. Bent B, Goldstein BA, Kibbe WA, Dunn JP. Investigating sources of inaccuracy in wearable optical heart rate sensors. *NPJ Digit Med*. 2020;3:18.
45. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;1(8476):307-310.
46. Someya T, Bao Z, Malliaras GG. The rise of plastic bioelectronics. *Nature*. 2016;540(7633):379-385.
47. Webb RC, Bonifas AP, Behnaz A, Zhang Y, Yu KJ, Cheng H, et al. Ultrathin conformal devices for precise and continuous thermal characterization of human skin. *Nat Mater*. 2013;12(10):938-944.
48. Imani S, Bandodkar AJ, Mohan AM, Kumar R, Yu S, Wang J, et al. A wearable chemical-electrophysiological hybrid biosensing system for real-time health and fitness monitoring. *Nat Commun*. 2016;7:11650.
49. Shao Y, Wang J, Wu H, Liu J, Aksay IA, Lin Y. Graphene based electrochemical sensors and biosensors: a review. *Electroanalysis*. 2010;22(10):1027-1036.
50. Labroo P, Cui Y. Flexible graphene bio-nanosensor for lactate. *Biosens Bioelectron*. 2013;41:852-856.
51. Lee H, Song C, Hong YS, Kim MS, Cho HR, Kang T, et al. Wearable/disposable sweat-based glucose monitoring device with multistage transdermal drug delivery module. *Sci Adv*. 2017;3(3):e1601314.
52. Chi YM, Jung TP, Cauwenberghs G. Dry-contact and noncontact biopotential electrodes: methodological review. *IEEE Rev Biomed Eng*. 2010;3:106-119.
53. Castaneda D, Esparza A, Ghamari M, Soltanpur C, Nazeran H. A review on wearable photoplethysmography sensors and their potential future applications in health care. *Int J Biosens Bioelectron*. 2018;4(4):195-202.
54. Buller MJ, Tharion WJ, Cheuvront SN, Montain SJ, Kenefick RW, Castellani J, et al. Estimation of human core temperature from sequential heart rate observations. *Physiol Meas*. 2013;34(7):781-798.
55. Koh A, Kang D, Xue Y, Lee S, Pielak RM, Kim J, et al. A soft, wearable microfluidic device for the capture, storage, and colorimetric sensing of sweat. *Sci Transl Med*. 2016;8(366):366ra165.
56. Bumgarner JM, Lambert CT, Hussein AA, Cantillon DJ, Baranowski B, Wolski K, et al. Smartwatch algorithm for automated detection of atrial fibrillation. *J Am Coll Cardiol*. 2018;71(21):2381-2388.

57. Acharya UR, Fujita H, Lih OS, Hagiwara Y, Tan JH, Adam M. Automated detection of arrhythmias using different intervals of tachycardia ECG segments with convolutional neural network. *Inf Sci.* 2017;405:81-90.
58. Rodbard D. Continuous glucose monitoring: a review of successes, challenges, and opportunities. *Diabetes Technol Ther.* 2016;18(S2):S2-3-S2-13.
59. Shah SA, Velardo C, Farmer A, Tarassenko L. Exacerbations in chronic obstructive pulmonary disease: identification and prediction using a digital health system. *J Med Internet Res.* 2017;19(3):e69.
60. Turakhia MP, Desai M, Hedlin H, Rajmane A, Talati N, Ferris T, et al. Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smartwatch: the Apple Heart Study. *Am Heart J.* 2019;207:66-75.
61. Ong MK, Romano PS, Edgington S, Aronow HU, Auerbach AD, Black JT, et al. Effectiveness of remote patient monitoring after discharge of hospitalized patients with heart failure: the Better Effectiveness After Transition–Heart Failure (BEAT-HF) randomized clinical trial. *JAMA Intern Med.* 2016;176(3):310-318.
62. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, et al. Effect of continuous glucose monitoring on glycemic control in adults with type 1 diabetes using insulin injections: the DIAMOND randomized clinical trial. *JAMA.* 2017;317(4):371-378.
63. Steventon A, Bardsley M, Billings J, Dixon J, Doll H, Hirani S, et al. Effect of telehealth on use of secondary care and mortality: findings from the Whole System Demonstrator cluster randomised trial. *BMJ.* 2012;344:e3874.
64. Piwek L, Ellis DA, Andrews S, Joinson A. The rise of consumer health wearables: promises and barriers. *PLoS Med.* 2016;13(2):e1001953.
65. Ancker JS, Edwards A, Nosal S, Hauser D, Mauer E, Kaushal R. Effects of workload, work complexity, and repeated alerts on alert fatigue in a clinical decision support system. *BMC Med Inform Decis Mak.* 2017;17(1):36.
66. Dowding D, Randell R, Gardner P, Fitzpatrick G, Dykes P, Favela J, et al. Dashboards for improving patient care: review of the literature. *Int J Med Inform.* 2015;84(2):87-100.
67. Gerke S, Minssen T, Cohen G. Ethical and legal challenges of artificial intelligence-driven healthcare. *Artif Intell Healthc.* 2020:295-336.
68. Ribeiro MT, Singh S, Guestrin C. Why should I trust you? Explaining the predictions of any classifier. In: *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*; 2016 Aug 13-17; San Francisco, CA. New York: ACM; 2016. p. 1135-1144.
69. Hathaliya JJ, Tanwar S. An exhaustive survey on security and privacy issues in Healthcare 4.0. *Comput Commun.* 2020;153:311-335.
70. Zhang R, Liu L. Security models and requirements for healthcare application clouds. In: *Proceedings of the 2010 IEEE 3rd International Conference on Cloud Computing*; 2010 Jul 5-10; Miami, FL. Piscataway: IEEE; 2010. p. 268-275.