Biomedical Materials & Devices
https://doi.org/10.1007/s44174-023-00113-9

REVIEW

A Review of Biomedical Devices: Classification, Regulatory Guidelines, Human Factors, Software as a Medical Device, and Cybersecurity

Felix Tettey[1,2] · **Santosh Kumar Parupelli**[1,2] · **Salil Desai**[1,2]

Received: 26 May 2023 / Accepted: 29 June 2023

Abstract
Biomedical devices provide a critical role in the healthcare system to positively impact patient well-being. This paper aims to provide the current classifications and subclassifications of hardware and software medical devices according to the Food and Drug Administration (FDA) guidelines. An overview of the FDA regulatory pathway for medical device development such as radiation-emitting electronic product verification, product classification database, Humanitarian Use Device (HUD), premarket approval, premarket notification and clearance, post-market surveillance, and reclassification is provided. Current advances and the advantages of implementing human factors engineering in biomedical device development to reduce the risk of user error, product recalls and effective safe use are discussed. This paper also provides a review of evolving topics such as the Internet of Things (IoT), software as medical devices, artificial intelligence (AI), machine learning (ML), mobile medical devices, and clinical decision software support systems. A comprehensive discussion of the first FDA-approved AI-medical device for the diagnosis of diabetic retinopathy is presented. Further, potential cybersecurity-related risks associated with software-driven AI/ML and IoT medical devices are discussed with an emphasis on government regulations. Futuristic trends in biomedical device development and their implications on patient care and the healthcare system are elucidated.

Keywords AI/ML/IoT · Cybersecurity · FDA · Human factors · Software as a Medical Device (SaMD)

Medical Devices

According to the United States (US) Food and Drug Administration (FDA), medical devices are any instrument, machine, contrivance, implant, and in vitro reagent besides drugs used for diagnostic and therapeutic purposes in humans or animals [1]. On the contrary, the World Health Organization (WHO) describes a medical device as any instrument, apparatus, machine, appliance, or another article, invented by the manufacturer to be used for specific medical purposes whose primary action is not achieved by immunological, metabolic, or pharmacological means [2]. In the United States of America, the FDA is responsible for the effectiveness and safety of medical devices. Within FDA, the Center for Devices and Radiological Health (CDRH) is largely liable for pre- and post-market regulation of medical devices in the United States [3, 4].

Material–tissue interactions are critical to the success of medical devices, and the demand for synthetic biomaterials in medical devices and tissue replacement applications is gradually increasing. Additive manufacturing has emerged as a feasible and novel solution to designing biomaterials for bulk and surface qualities that aim to enhance the performance of 3D-printed medical devices [5–13]. The Global Unique Device Identification Database (GUDID) lists over 2.2 million items; however, approximately 500,000 distinct forms of medical devices exist globally. The medical device industry is rapidly evolving through technological disciplines such as materials science, electronics, microtechnology, and nanotechnology [14]. Some notable medical devices include catheters, bandages, tomography machines, long-term surgical implants, magnetic resonance imaging (MRI) machines, X-ray machines, surgical gloves, artificial hips and knees, bipap ventilator, hemodialysis machine

✉ Salil Desai
sdesai@ncat.edu

1 Industrial and Systems Engineering Department, North Carolina Agricultural and Technical State University, Greensboro, NC 27411, USA

2 Center of Excellence in Product Design and Advanced Manufacturing, North Carolina Agricultural and Technical State University, Greensboro, NC 27411, USA

Published online: 01 August 2023

usage, ultrasound scanner, blood bank centrifuge with accessories, and many more.

Classification of Medical Devices by the FDA

The FDA is the oldest consumer protection agency in the United States (US) that categorizes medical devices by their purpose and medical specialty. The FDA-Unique Device Identification and the electronic health record (EHR) list the medical device types, with their examples [15]. The medical devices by their purpose entail cosmetic devices used to improve the appearance and the dermal filler is a typical example [16]. Home health and consumer devices are another type used by consumers, which include contact lenses, needles, and syringes. Implants and prosthetics devices are the devices or tissues placed inside the body or periphery. Examples include breast implants, cochlear implants, and cerebral spinal fluid (CSF) shunt systems.

General hospital devices and supplies by purpose are the groups of devices that healthcare professionals broadly use to support patient care. This involves infusion pumps, hospital beds, and sterilization systems and includes liquid chemicals and ethylene oxide. Apart from medical devices grouped by purpose, the FDA also has medical devices grouped by specialty, such as cardiovascular, dental, neurological, and pediatric devices [16]. The FDA ultimately puts all these devices into classes (Classes I, II, and III) to reflect the device's risks as illustrated in Fig. 1. The FDA scrutinizes any device that poses a potential danger and differs from a previously approved device.

Class I

These devices are simpler in design compared to other classes. They are low-risk devices with only the most essential safeguards to ensure their safety and performance. They are subject to fundamentals or no regulations at all because these devices are neither life-saving nor life-threatening and do not pose an undue risk of illness or harm [18]. The classification regulations of 21 CFR (Code of Federal Regulations) of the FDA shows that about 47% of medical devices are in this class of device and 95% of these devices are exempt from regulatory process [19]. This list is compiled in the Medical Device Exemptions document. Class I devices include gloves, bandages, wraps, exam gowns, face masks, crutches, oxygen mask, tongue depressors, scissors, electric toothbrushes, hospital beds, surgical sponges, and reusable surgical scalpels and surgical masks [20, 21].

Class II

These devices are generally medium-risk devices, and it is made up of a single class compared to the European Union medical device regulation, which is further divided into Class IIa, which are medium-risk devices , and Class IIb, which are medium-to-higher-risk devices [22]. Forty-three percentage of medical devices fall in this class [19]. These

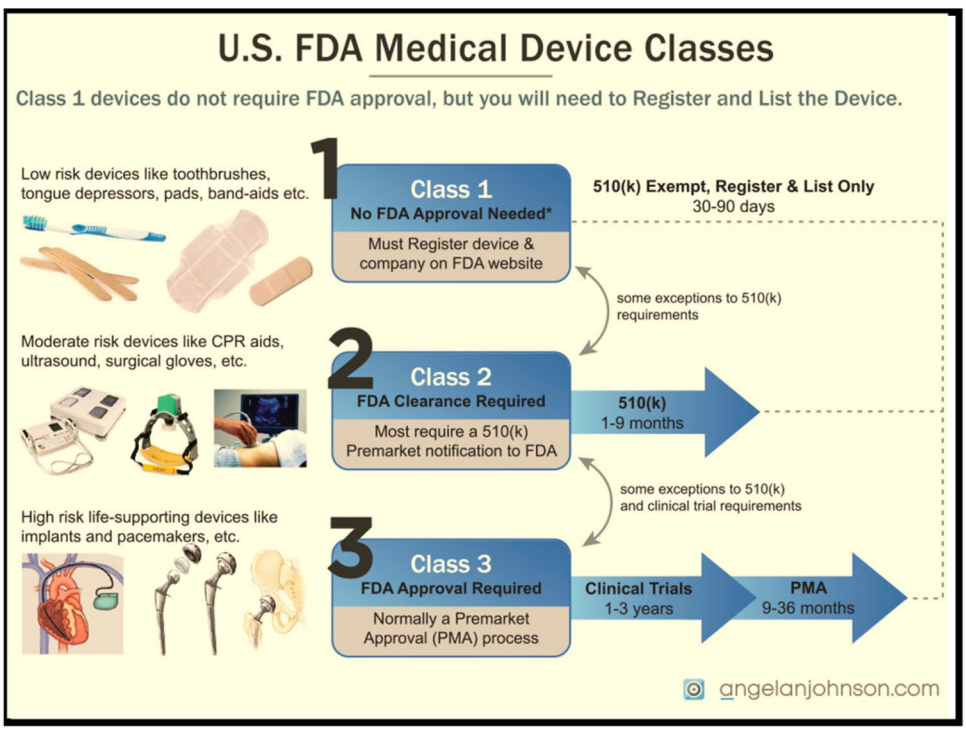

Fig. 1 Medical device classes as per US FDA [17]

devices are subject to general and special controls that must give adequate safety and eficacy and clarify how these controls provide such assurance. Such devices include hypodermic needles, blood bags, colostomy bags, suction catheters, and syringes, wheelchairs, surgical masks, surgical drapes, catheters, X-ray machines, MRI machines, blood pressure cuffs, pregnancy test kits, blood transfusion kits, contact lenses, diagnostic endoscopes, electrocardiogram (ECG) monitors, and colonoscopes [20].

Class III

These devices with the most significant risk are subjected to various general and specific controls to ensure their safety and eficacy. 10% of the medical devices regulated by the FDA fall under this category [19]. These device classes are primarily invasive such as body orifice, surgically invasive, and implantable entities. Class III devices require premarket approval (PMA) and other critical steps before being licensed [23]. These devices need to go through an extensive clinical trial to demonstrate their safety and effectiveness. Examples of devices in this class include implanted pacemakers, heart valves, silicone implants, hip and bone implants, implanted prosthetics, wearable automated external defibrillators, and high-frequency ventilators [20].

Invasive Devices

A medical device is said to be implantable if surgically or medically it is either entirely or partially launched into the human body and is meant to stay there temporarily or permanently after the process [24]. A few implants are made from skin, bone, or other body tissues, whereas most others are from plastic, ceramic, metal, or other materials. Some examples of implants include breast implants, cochlear implants, craniofacial implants, dental implants, metal on metal hip implants, and urogynecological surgical mesh implants. Implants such as stents or hip implants can be set to function permanently, whereas others, such as screws to repair broken bones, can be taken out once they are not required. Medical implants include surgical dangers during placement or discharge, infection, and implant failure. Invasive devices make patients seven (7) times more likely to obtain hospital infection [25, 26]. Skin antiseptics such as 2% chlorhexidine gluconate with 70% isopropyl alcohol have been recommended to be frequently employed to reduce the chances of infections before a device is implanted in the body [27, 28]. The critical invasive devices associated with increased infection rates in intensive care unit (ICU) settings include endotracheal tubes (ETT), urinary catheters (UC), and central venous catheters (CVC) [29]. Patient approval is pertinent before inserting a device, except for situations where the patient cannot consent. Insertion and removal of an invasive device needs documentation showing details of the person who inserted it, the date, time, and site of insertion, and the level of sterility used for insertion or removal. Furthermore, some high-risk devices are frequently checked for signs of infection and removed once they are no longer needed [26, 30]. Also, some devices must be removed after a period to avoid a considerably increased risk of infection due to breeding by microorganisms, which quickly develop into a biofilm leading to profound suffering [31–35]. A few individuals may have reactions to the materials utilized in implants. Surgical techniques can lead to bruising at the surgical location, swelling that comes with redness, and pain. Two critical biocompatible film technologies have been advanced to support the succession of implantable biomedical devices. These include the improvement of bioinert/biocompatible coverings for encapsulation of silicon chips implantable in the human body (e.g., retinal prosthesis implantable in the human eye) and the development of biocompatible films with the high-dielectric constant and micro-fabrication process to yield energy storage supercapacitors entrenched in the microchip to attain complete miniaturization for implantation into the human body [36].

Non-invasive Device

A non-invasive device is any symptomatic apparatus or device that does not include the penetrating or opening of the skin or that does not introduce an unfamiliar object or material into the body. Some advantages of non-invasive devices or procedures for patients are that they lower the risk of infection, reduce trauma, accelerate recovery, and reduce the cost of hospital stays and medical treatments. A non-invasive device such as an electronic skin patch senses excess glucose in sweat [37]. It automatically administers drugs by heating micro-needles that saturate the skin, as shown in the diagram in Fig. 2a. A non-invasive Vascular Wall Motion (VWM) monitoring system, made up of a pulse radar sensor and support vector machine (SVM) classification algorithm, has been developed to detect access flow dysfunction in Arteriovenous Fistula (AVF) [38]. An easy-to-use, non-invasive, and cost-effective biodevice for detecting chronic kidney disease (CKD) is essential for large-scale screening and reducing undiagnosed CKD [35]. The estimated glomerular filtration rate (eGFR), derived from serum creatinine, is used to diagnose, or stage CKD [39]. Invasive methods are required to get serum creatinine, an excellent limitation for screening and monitoring CKD outside the hospital. Since most patients with early-stage CKD are asymptomatic, the early diagnosis is dificult if a blood test is not performed [40]. Deep brain stimulation surgery, among other procedures, can provide durable tremor control. However, their utilization is minimized due to high costs, patient and practitioner preferences, and perceived high

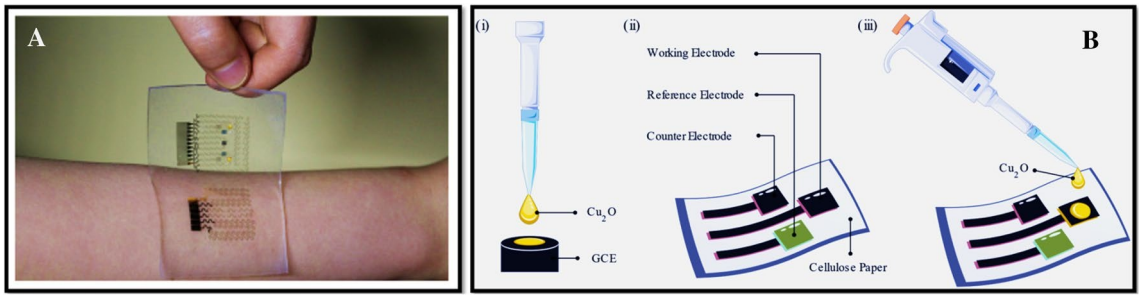

Fig. 2 **a** A non-invasive electronic skin patch that senses excess glucose in sweat and administers drug spontaneously by heating microneedles [47], **b** schematic construction of the glucose sensor. (i) Cu_2O nanoclusters drop cast on the GCE for material study. (ii) Graphene paste printed on cellulose cloth with an Ag/AgCl reference electrode (RE). (iii) Modified WE with Cu_2O on the graphene printed cellulose substrate [48]

risks. The International Parkinson and Movement Disorder Society's (IPMDS) task group defines tremors as involuntary, rhythmic, and oscillatory movements of a body part [41, 42]. Medical devices are positioned uniquely to bridge this gap between lifestyle interventions, pharmacotherapies, and surgical treatments to provide safe and effective tremor suppression. These devices are primarily non-invasive, benefiting the patient's existing pharmacotherapy and lifestyle intervention. Some of the major challenges of non-invasive devices include accuracy, usability, and applicability [43]. For example, in the case of glucose monitoring non-invasive devices, the indirect nature of measurement and physiological time lag between tissue glucose and the blood leads to reduced accuracy and low usability. The usability of non-invasive devices for usage in homes and ofices, in terms of their simplicity and ultra-portability while adopting a human factor perspective, is another essential concern. Non-invasive devices have a limitation of adequate health data security especially with the complex technologies' incorporation. Furthermore, non-invasive smart implants have drawbacks such as lack of policies controlling their use, privacy concerns, and limited memory space [44]. Biosensing devices well equipped can be adopted to continuously monitor and improve glucose monitoring. Research is ongoing for an easy and less-invasive way to measure glucose daily using tears, airway mucus, sweat, saliva, or the interstitial fluid of subcutaneous tissue.

Biosensing Device

Portable or wearable devices are being extensively explored to improve the comfort level of patients, especially those affected with diabetes and sometimes chronic wounds [45]. New sensors are capable of monitoring glucose levels effortlessly and are also economically stable. The current glucose monitoring devices are minimally invasive and assess real-time interstitial fluid glucose levels; however, they do not do this without relying on skin piercing, with many spots lasting about ten days or less [46]. Also, most non-invasive devices incorporate complex technologies that rely on optical or spectroscopy techniques. Fabiane Fantinelli Franco et. al., developed a non-invasive, portable sweat-based glucose sensor constructed by hand printing graphene paste electrodes on sustainable biodegradable and biocompatible cellulose substrates to overcome some challenges. Cu_2O nanoclusters were utilized as the sensitive material and drop cast on top of the working electrode (WE) to achieve the affordable, voltametric glucose sensor as shown in Fig. 2b. The Cu_2O nanomaterial demonstrated good trait toward glucose detection in primary medium. The non-enzymatic disposable Cu_2O-based sensor for portable glucose detection was successful.

Wearable biosensors have generated the potential to analyze biochemical markers continuously and accurately in biofluids like sweat, tears, saliva, and interstitial fluid [49]. Wearable biosensor technology would significantly impact our daily lives if it could accurately and consistently sense physiological data in real time. A biosensor is developed for salivary conductivity in detecting chronic uropathy. The prevalence of chronic uropathy is increasing, and it brings an unlimited healthcare burden. The standard measurement of kidney function needs invasive blood tests, which hinders the first detection and causes low awareness of CKD. A tool with miniaturized coplanar biosensing probes for measuring salivary conductivity at a coffee volume (50uL) has been designed. Early results from a recent study showed that patients with CKD had considerably increased salivary conductivity. This tool functions as a surrogate marker for kidney function. This real-time, non-invasive, and easy-to-use portable biosensing device is also reliable for screening CKD. Electrochemical voltametric sensors are several of the foremost hopeful sensors for monitoring various physiological analytes because of their performance and portability. Voltametric sensors distinguish themselves from others due to their reduced analysis time ability, selective sensing, and cost-effectiveness. A biosensor has been used for tremor

suppression. Tremors are the foremost prevalent movement disorder that interferes with the patient's daily living and physical activities, ultimately resulting in a reduced quality of life. Surgical interventions like deep brain stimulation can provide durable tremor control. However, their utilization is minimized because of high costs, patient and practitioner preferences, and perceived high risks.

3D-Printed Bio-Medical Device Development

Additive manufacturing popularly known as 3D printing, is advancing steadily where the material is placed sequentially in a layer-by-layer fashion to build the functional 3D objects [50]. The 3D-printing technique provides flexibility in terms of customized patient-specific devices, design freedom, and complex internal structures [51–55]. Innovators have used three-dimensional (3D) printing in the medical device industry to create devices with unique composition, structure, and customizability [56–62]. This includes patient-specific craniofacial implant application for skull and facial skeleton reconstruction, titanium hip, and mandibular prosthesis, and scaffolding for tissue engineering [63]. Commercially available 3D-printed medical devices include implants, external prostheses, and instrumentation [64].

Recently, the FDA responded to a growing trend of 3D-bio-printed medical technologies and provided a more comprehensive regulatory pathway for technologies in this area with an issuing of new guidance advising on the technical aspects of manufacturing 3D-printed medical devices [71]. In 2016, FDA released a draft guidance document titled "technical considerations for additive manufactured medical devices' to outline the technical considerations, testing, and characterization recommendations for 3D-printed devices [65]. 3D-printing technologies also include direct-write methods such as inkjet printing with different biomaterials [72–79]. Metal 3D-printing technique enables the manufacturing of biomimicking implant devices with similar properties compared to natural bone. Figure 3 illustrates the various types of biomimicking implants fabricated using metal 3D printing [66]. The trachea-bronchial splint (TBS) is an example of a 3D medical device that employs patient-specific computer-aided design (CAD) developed to treat Tracheobronchomalacia (TBM), a juvenile disorder in which the primary airways collapse excessively during respiration. Traditional medicines have limitations in rare severe cases, resulting in high rates of treatment-related and disease-related morbidity and mortality [80]. The 3D-printing process of the tracheobronchial splint (TBS) is described in Fig. 4.

Even though there are many challenges such as reliability, sterilization, materials, and reproducibility of 3D-printed biomedical devices that still need significant attention, the current advancement so far has overcome enormous

Fig. 3 3DP implants: craniofacial plate implant Ti–6Al–4V DMLS [64], mandibular implants [65], spinal [66] and sternum [67] implants, lumbar cage [68], hip [69], and knee implants [70]. Reprinted under copyright CCBY-NC-ND 4.0 license

obstacles to bring numerous possibilities to life. The advancement of 3D-printing techniques has enabled the fabrication of novel biomedical devices with complex structures as illustrated in Figs. 3 and 4. The continued development and synthesis of regulation and technology will eventually determine the maturity of 3D printing within the biomedical sector [47, 81–85]. The FDA-approved biomedical devices that are currently in service include Osteofab craniofacial patient-specific stabilization device, DENTCA three-dimensionally printed polymer dentures, and TirboLOX-L titanium lumbar cages for spinal stabilization manufactured by Captiva Spine. An outline of the most relevant 3DP processes for biomedical applications is shown in Table 1.

4D Printing of Biomedical Devices

The merging of shape-morphing materials and additive manufacturing is promising for developing customized medical devices. The ability to convert 3D objects from one shape to another right off the print bed is 4D printing. Shape memory thermosets can be designed to have a collection of thermo-mechanical properties that can be advantageous to medical devices. However, their insolubility and inability to flow like resin are a challenge in processing them. The ability to resolve this challenge will be of great benefit to the development of this merger. Zarek et al. strategized to exploit a series of medical imaging modalities to construct a printable shape memory endoluminal device characterized by a tracheal stent. Based on anatomical data, a methacrylate

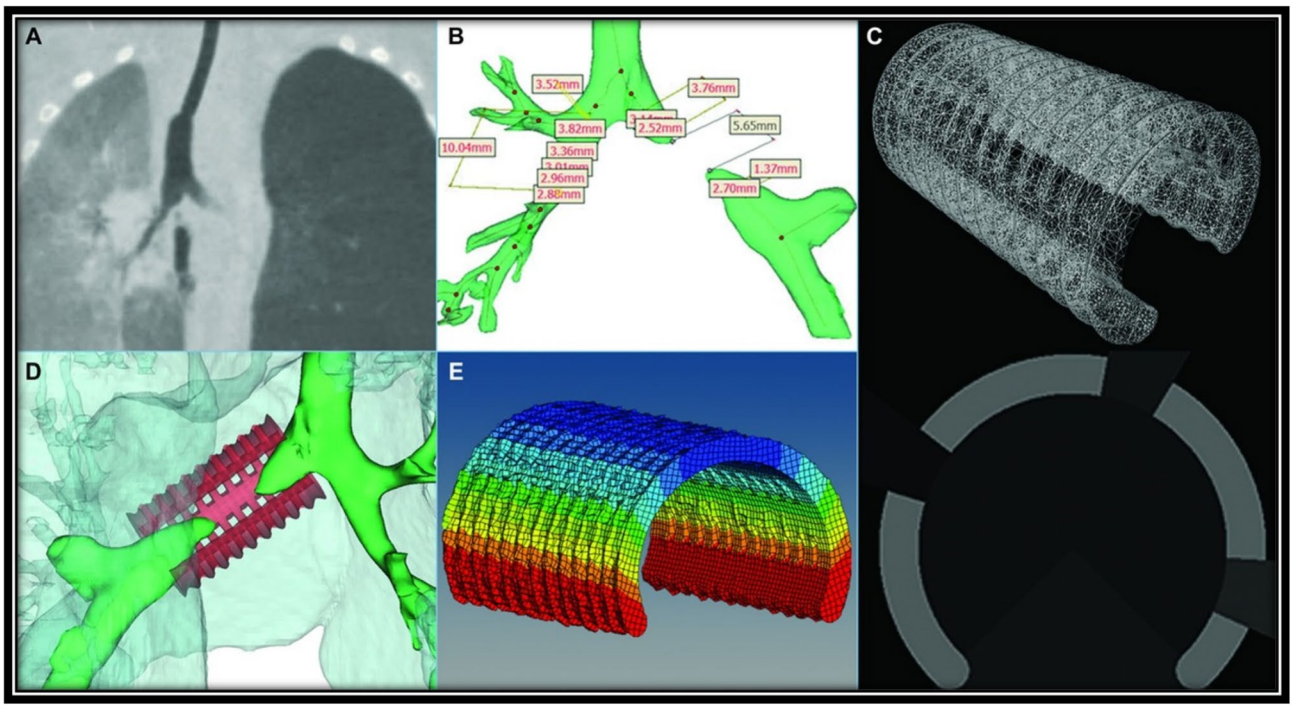

Fig. 4 The design process of the tracheobronchial splint (TBS). **A** Imaging of the airway using computed tomography (CT) to describe the location and severity of the disease. **B** DICOM images from the CT scan are utilized to make a 3D model of the patient's airway within Mimics (Materialized), where measurements are accomplished to produce design inputs of the device. **C** Design inputs are directed into a proprietary MATLAB (MathWorks) code which produces a series of 2D. TIFF images (image represented at the top). These are imported into Mimics and used to generate a STL of the device design (bottom). **D** Verifying performance requirements is done by virtually fitting the 3D model of the device over the 3D model of the patient's airway model to ensure an accurate fit. **E** Authentication of functional conditions is done by changing the STL of the device into a volumetric mesh and executing finite element analysis (FEA) in ANSYS (Ansys Inc) to ensure appropriate mechanical behaviors [50]

Table 1 Biomedical applications of different 3D-printing methods [86]

ASTM 3D-printing method	Biomedical applications
Powder-Bed Fusion (Metals, Ceramics, and Polymers)	Metals: Manufacturing titanium and cobalt-based alloys for hip or knee arthroplasty (i.e., structural applications). Ceramics: Manufacturing calcium phosphate bone scaffolds with designed porosity and complexity. Polymers: Manufacturing surgical models and tools with high accuracy
Directed Energy Deposition (Metals)	Manufacturing and testing different powder compositions and creating functionally graded materials and structures. Used for coatings and surface modifications
Material Jetting (Polymers and Composites)	Multimaterial or multicolor structures for surgical or visualization applications
Vat Polymerization (Stereolithography) (Polymers and Polymer/Ceramic Composites)	Drug delivery/discovery, surgical models
Material Extrusion (Ceramics, Polymers, and Bioinks)	Manufacturing ceramic bone scaffolds, surgical models (fused deposition modeling), drug delivery, and tissue regeneration (bioprinting)

polycaprolactone precursor with a molecular weight of 10,000 g mol^{-1} was printed with an ultraviolet light-emitting diode (UV-LED) stereolithography printer. This approach sought to converge with the zeitgeist of personalized medicine, anticipating that it would broadly expand the application of shape memory-exhibiting biomedical devices to numerous clinical indications [87].

One of the first medically applicable uses for 4D-printed constructions is in vascular regeneration and vascular stents since their tubular structure is easily obtained through a 4D rolling or stretching procedure. Figure 5 illustrates the recent developments of 4D printing of vascular graft and stent devices. The development of minimally invasive medical devices is aided by the ease with which 4D-printed vascular

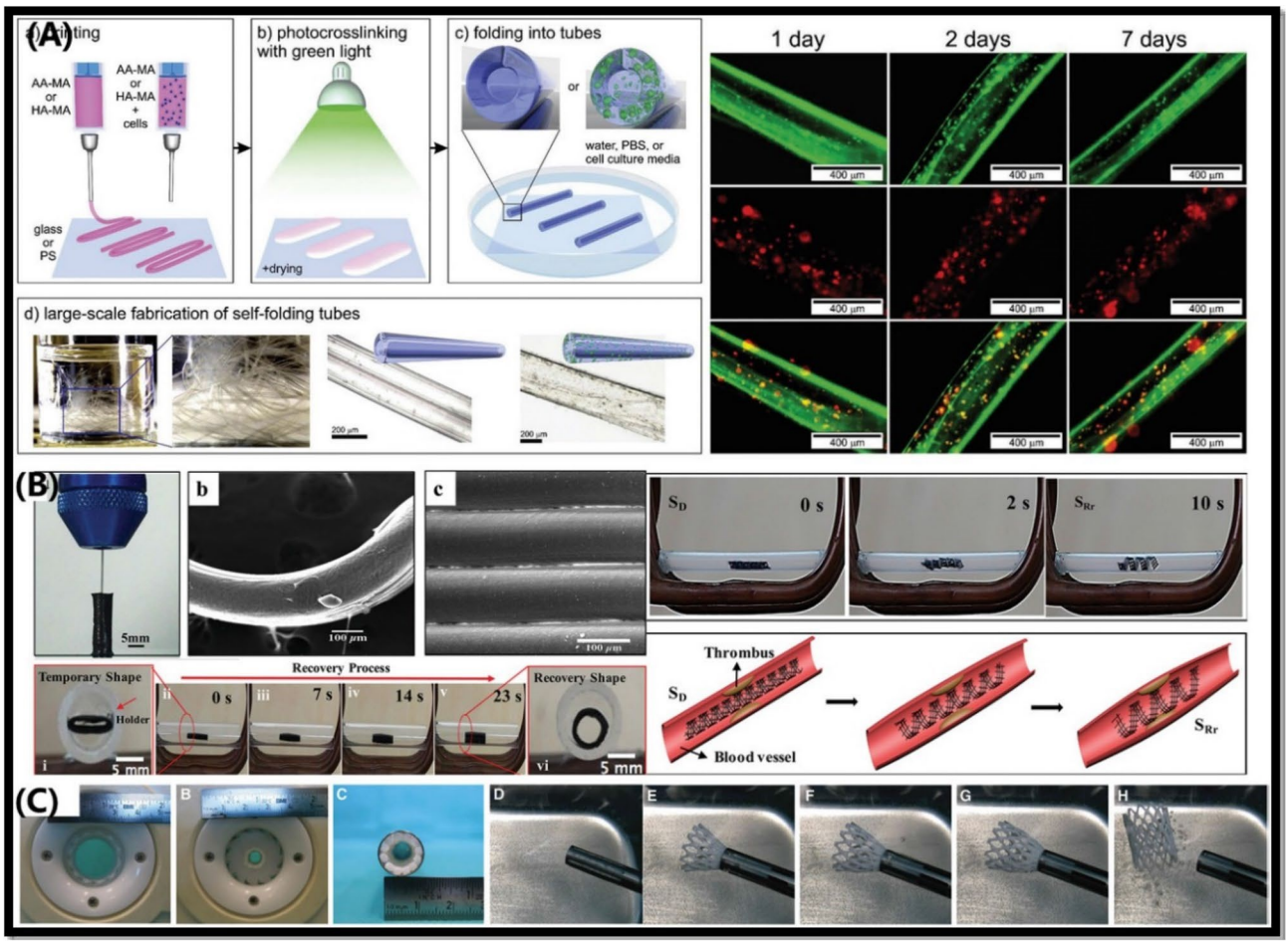

Fig. 5 4D vascular graft and stent devices. **A** Schematic of the DIW-printed AA-MA or HA-MA polymer membrane, which can self-fold into tubes in water, PBS, or cell culturing medium. The representative fluorescent images of the cell-laden self-rolling tubes in which live cells (green) and dead cells (red) are stained after 1, 2, and 7 days of culture and exhibited favorable tube formation. Reproduced with permission [88, 89] Copyright 2017, Wiley-VCH. **B** A thermos-responsive vascular stent was applied for vascular regeneration showing that the nascent fiber-based vessel scaffold could mimic the microstructure of native arteries. Reproduced with permission [90] Copyright 2017, American Chemical Society. **C** Crimping and delivery of 4D-printed vascular stent prototype. The printed stent was placed inside the crimpling device and then transferred into the transapi-cal delivery device. After being pushed out of the delivery system, it could self-expand. Reproduced with permission [91]. Copyright 2017, Mary Ann Liebert, Inc [92]

tissues and vessels can be easily implanted by utilizing dynamic shape transformation. Ionov et al. research group has demonstrated the fabrication of hollow self-folding 4D vascular tubes as shown in Fig. 5A by DIW printing using shape-morphing biopolymer hydrogels which include methacrylated hyaluronic acid and methacrylated alginate (HA-MA and AA-MA, respectively). The results of this study reported the fabrication of dynamically adjustable complex 4D structures using biodegradable shape-changing polymer–cell structures with tunable response and functionality. A stimuli-responsive vascular 4D stent was developed in a research study as shown in Fig. 5B for remote manipulation of the magnetic field-triggered 4D stent. In this study, Wei et al. research work demonstrated the direct-write printing of a vascular 4D scaffold by shape memory polymers (SMPs: PLA ink) and shape memory nanocomposites (SMNCs: Iron oxide (Fe_3O_4)). The shape recovery process of the vascular 4D scaffold was triggered by the addition of the Fe_3O_4 nanoparticles which enabled remotely actuated and structure-magnetically guided behavior. Cabreraet et. al., research group proposed a proof-of-concept study utilizing the fused deposition modeling 3D-printing technique to implant 4D-printed biocompatible polymer stents with self-expandable properties for minimally invasive heart valve regeneration as shown in Fig. 5C. In this study, a flexible thermoplastic copolyester elastomer was utilized due to its biodegradability and biocompatibility nature. The results of this study demonstrate the fabrication of a polymer stent with mechanical properties similar to those of traditional nitinol stents used in animal trial studies for heart valve

implantation. Advanced biomedical devices which include biosensors, bionic ears/eyes, and biorobots that have a significant impact on the future of biomedicine can be developed with the combination of 3D- and 4D-printing methods.

Regulatory Pathways for FDA Medical Devices

Radiation-Emitting Electronic Product (R-EEP) Verification

Prior to advancing the device to the regular classification steps, the FDA verifies whether it's a R-EEP or not. The FDA defines R-EEP as any electrically driven product that can produce any type of radiation on the electromagnetic spectrum. These products are regulated by the FDA to prevent unwanted exposure to radiation. When the product also functions as a medical device, the medical device regulations must be strictly followed. Apart from MRI devices, laser toys, laser pointers, liquid crystal displays (LCDs), mammography devices, and light-emitting diodes (LEDs), most radiation-generating equipments are not classified as a medical device [93]. Any medical claim made, however, about a product as a medical device is subject to the FD&C Act's medical device provisions, as well as the radiation-emitting product restrictions. The FDA demands the submission of product reports and the retention of records for specific radiation-emitting equipment [94].

Product Classification Database

A device's classification is determined by its anticipated use and potential risk of use. Classification of the devices can be determined by using the classification database or searching through the device panel (medical specialty) to which the device belongs and going directly to the listing for the panel to ascertain one's device and the corresponding regulation. Over 1700 different types of devices have been classified and characterized by the FDA, and they are divided in the Code of Federal Regulations (CFR) into 16 medical specialty "panels" such as Dental, Orthopedic, and Toxicology specialties and their regulation citation number as listed in Table 2.

Parts 862 through 892 of the CFR contain these panels. The CFR provides a broad description of each device classified by the FDA, including the intended purpose, the device's class (Class I, II, or III), and information about marketing requirements. Medical devices must meet the requirements of 21 CFR 862-892, a classification rule [18]. To identify a device using the classification database, first locate the regulation number, which is the classification regulation for your device, by searching the classification database for a portion of the device name, or by typing directly into the Code of Federal Regulations (CFR) and reading through the list of classified devices, or if uncertain, use the keyword directory in the CFR Product Code Classification Database. The CDRH developed the Product Classification Database which contains medical device names and their related product code information. For FDA, the device name and product code connect the generic class of a device. A device's Product Code is its unique identifier and is defined by 21 CFR Parts 862-892. These files are updated every Sunday [96]. The CFR begins each classification panel with a list of devices that are categorized in that panel. 21 CFR 880.2920-Clinical Mercury Thermometer is an example of classified equipment having a 7-digit number. Once the device in the panelist is found as the 7 digits above, click for more description of the device and as such with the example above, it is categorized as Class II. Likewise, multiple entries for various sorts of thermometers can be found in the Classification Database under "thermometer." The classification number used on the Medical Device Listing form is the three-letter product code FLK in the database for Clinical Mercury Thermometer.

Table 2 Medical specialty of devices with their abbreviations, regulations code location [95]

Panel/medical specialty	Abbreviation	Regulation citation (21 CFR)
Anesthesiology	AN	Part 868
Cardiovascular	CV	Part 870
Chemistry	CH	Part 862
Dental	DE	Part 872
Ear, Nose, and Throat	EN	Part 874
Gastroenterology and Urology	GU	Part 876
General and Plastic Surgery	SU	Part 878
General Hospital	HO	Part 880
Hematology	HE	Part 864
Immunology	IM	Part 866
Microbiology	MI	Part 866
Neurology	NE	Part 882
Obstetrical and Gynecological	OB	Part 884
Ophthalmic	OP	Part 886
Orthopedic	OR	Part 888
Pathology	PA	Part 864
Physical Medicine	PM	Part 890
Radiology	RA	Part 892
Toxicology	TX	Part 862

Humanitarian Use Device (HUD)

The FDA established the HUD pathway to entreat inventors to maximize the creation of devices to fight unusual diseases.

The HUD pathway allows the applicant to develop a medical device with an expedited process and decisions made to the applicant within 45 calendar days. To acquire HUD designation, the inventor must submit supporting data to the FDA establishing the rareness of a condition that affects fewer than 4000 patients in the United States each year.

Premarket Approval

PMA is therefore the FDA's procedure for scientific and regulatory evaluation to assess the effectiveness and safety of Class III medical devices. All devices in such a category require a PMA application under section 515 of the FD&C Act for marketing authorization. Such devices must meet the conditions of the FDA such as 1–3 years clinical trial before approval. In the trial, safety data are generated which includes scientifically proven traces of effectiveness. Blood establishment devices which are the devices that deal with blood, blood products, and cellular therapies as well as the integral association of specific medical devices with these biological products are regulated by The Center for Biologics, Evaluation, and Research (CBER). This regulation also includes medical devices related to blood collection and processing procedures.

Premarket Notification and Clearance

The sort of premarketing submission/application necessary for FDA permission to market is determined by the device's class. Any device which is of human use and does not require premarket notification and PMA will request submission of a 510 (k) to FDA but will not if the device is as well exempted from 510(k) requirements. A 510(k) is a premarket submission made to the FDA to demonstrate that the device to be advertised is as safe and eficient as a legally marketed device. When a more specialized indication is added to the device's labeling, such as "for making holes in the skin," the subcategory of intended use is created and as such, the use instructions are either located on the device's labeling or presented verbally during the product's sale. Submitters must make and justify their substantial equivalence claims by comparing their product to one or more similarly constructed, legally marketed devices. A legally marketed device is a device that has been found to be safe and eficient through the 510 (k) process, has been reclassified from Class III to Class II or I, and has been given marketing authorization through the De Novo classification process under section 513 (f)(2) of the FD&C Act, or has been legally marketed before May 28, 1976 (a pre-amendments device). These devices are also not exempt from the premarket notification requirements. A submitter may only proceed to market the device in the US when an order declaring device safe and eficient is received. The device's safety and effectiveness determination are usually made within 90 days (about 3 months) depending on the details submitted [97].

Post-Market Surveillance (PMS)

The United States Food and Drug Administration defines post-market surveillance as "the active, scientifically valid collection, systematic, analysis, and interpretation of the data or other information about a commercially available product." By observing and analyzing daily or periodic practical usage, post-market surveillance aims to continuously verify a medical device's benefits and identify previously unknown risks. Post-market surveillance (PMS) is a legal requirement for medical device manufacturers to collect and evaluate the data from the use of their products in a specific market. Maintaining a PMS system is important not only to handle the regulatory requirements but also to enhance the risk management and potentially improve the standard of the device. Although premarket product and quality management system (QMS) compliance receive much attention from manufacturers who want to determine themselves in their target markets, successful commercialization also requires viable PMS efforts [98].

Reclassification

Even though devices are classified into one of three regulatory classes: class I, class II, or class III, the regulatory class of a device type can be modified through the reclassification process. The primary goal of reclassification is to apply the appropriate level of regulatory controls to a device based on the most recent data on its safety and effectiveness. Except for devices currently classified as class III under section 513 (f)(1), the FDA may prompt or respond to a petition for reclassification of a device type from an interested person. In either case, the emergence of new information about the device serves as the basis for reclassification. Under section 513 (e), the FDA may issue a final order reclassifying a device for the following.

> The FDA posting a proposed order for reclassification in the Federal Register based on reliable scientific data concerning the device, such as its benefit to public health, its nature, and, if established, the likelihood of risk associated with using the device, as well as The FDA calling a meeting of a device categorization panel. The FDA is considering any comments submitted during the time allotted for doing so to the public docket for the proposed order [99].

Medical Device Accessory

A parent device execution is supplemented with or improved by one or more accessories. An accessory is a device designed to support or enhance the performance of one or more parent devices [100]. Also, a component is any raw material, substance, piece, part, software, firmware, labeling, or assembly perceived as part of the finished, packaged, and labeled device [101]. An infusion pump system, for example, is made of the infusion pump as the parent device and the stand as the accessory, as shown in Fig. 6. By enabling the infusion pump to store medications and beverages at an ideal height and within easy reach of the patient or caregiver, the stand in this system serves as an accessory that supports the infusion pump's functionality. The FDA utilizes the same criteria used for any device classification to assess the risk of accessories and the regulatory controls required to assure their effectiveness and safety. An Accessory Classification Request, a printed request, is submitted to the FDA Federal Food, Drug, and Cosmetic Act (FD&C Act) under section 513 (f)(6) to request the appropriate classification for an existing or new accessory type. A new accessory type of request should be submitted together with the parent device submission and supported with a cover letter listing a clear indication that the submission includes a "New Accessory Request" and identification of the proposed classification of the accessory (i.e., whether it belongs to class I or class II). Also, the necessary information to establish the risk tendency of the accessory when used with the parent device is required. A request for an existing accessory type also follows the exact requirement as the new one. When an Accessory Classification Request is approved, the FDA will issue a final classification order in the Federal Register, notifying the public of the decision and the accessory type's classification. If the FDA disagrees with the categorization recommendation offered in a request, the submission and related decision will not be made public, but the submitter will get a written response explaining why the request was denied.

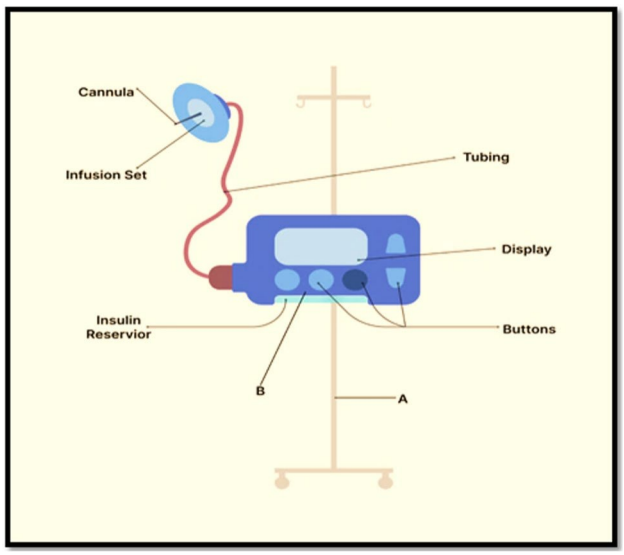

Fig. 6 The sketch represents the infusion pump system. (A) The stand as the medical device accessory, (B) the parent device

Human Factors Engineering of Medical Device

Human factors are a discipline that concentrates on the interactions between people and devices with emphasis on hardware and software design that is compatible for the user and effects usage. Human factors engineering (HFE) or usability engineering is the application of human factors in the designing of equipment or devices for easy, effective, and safe use by people [102]. The Center for Devices and Radiological Health (CDRH), of the FDA, expands and executes national programs and regulations to protect the public with respect to medical and radiological devices. An evolving concern of CDRH is the implementation of good human factors practices in the design of medical devices. The use of good user interface design principles and participation of healthcare practitioners in design analysis and tests plays a crucial role in terms of safety and cost reduction to healthcare facilities. HFE is employed not only in the design of the devices but also in the assessment of medical devices using techniques that improve the evidence-based practice which generally increases patient safety [103–105]. The considerations in the design of medical devices involve the device user, device use environments, and the device user interface as shown in Fig. 7. The device user's ability to operate a medical device depends generally on the design and personal characteristics of the user such as sensory abilities (vision, hearing, cognitive abilities, tactile sensitivity), literacy and language skills, overall physique (size, strength, flexibility,

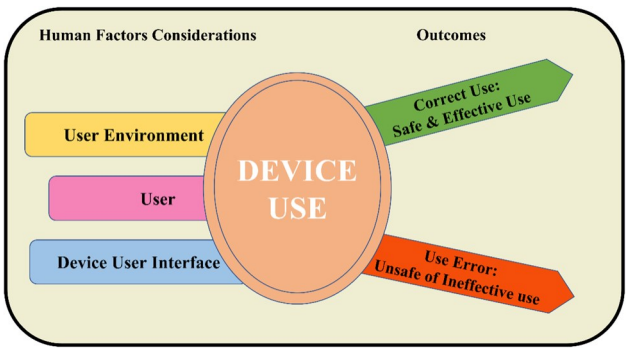

Fig. 7 Medical device design considerations (US FDA)

and coordination), level of education, and the general knowledge of similar types of devices (willingness to learn and adapt to new devices). Human factors utilization in medical devices has a lot of significant benefits. It reduces user training, retraining, and reliance on user manuals. It also reduces the risk of user error, harm, and risk of product recalls. Additionally, there is a better user understanding of the device's operation, since there are improved controls and improved display interfaces (U.S.FDA). For a successful application of human factors in medical devices, it is important to understand and consider how people recognize information and how they interpret the information from the device on what to do and how they operate or control the device components. Also, the understanding of how the device receives input from the user and responds with feedback especially on the actions is relevant to consider in designing medical devices. The errors and dangers associated with the use of medical devices can be prevented or reduced using the "prevention through design" which involves the critical use of human factors design processes such as the preliminary analysis, formative design evaluation and modification, and the design validation [106].

Current advances in HFE applications have facilitated the design of mobile dialysis device prototypes with the most recent prototype of a mobile dialysis device increasing functionality, which implies that human factors concern (e.g., eficiency, bulkiness, and weight) are critically considered now. One latest advance is the design of an Ambulatory Kidney to Improve Vitality (AKTIV), using an interview protocol during the early stages of product development to capture patients' and caregivers' reactions. The AKTIV can enhance patients' life quality and reduce mortality rates [107]. Manufacturers of interactive medical devices like infusion pumps have adopted the use of mediating representations to guarantee that devices minimize the danger of inadvertent injury during use [108]. Designing for safety and usability requires the use of artifacts like personas and scenarios, which are known to integrate viewpoints from various perspectives [109]. Companies are focusing more on the effects of device design, particularly user instructions, on the performance of health professionals and lay users who use medical devices. The FDA is keeping an eye on human factors issues as part of its site inspections, premarket device approvals, and post-market incident evaluations [110]. The human factors evaluation of the medical devices such as infusion pumps was conducted in two (2) phases by Gill Ginsburg [111]. The first phase was a heuristic evaluation of each pump according to 4 sets of criteria. The first criteria were formed with fifteen (15) human factors principles adapted from human factors principles developed by Nielson [112] and Schneiderman [113]. This study demonstrates the need of carrying out both phases—a heuristic assessment phase and a user testing phase—in a human factor's evaluation of medical devices because they both complement one another and provide crucial details. The heuristic evaluation phase identifies design elements that might be troublesome for users and result in mistakes or frustrations, but the likelihood and severity of those mistakes can only be seen through user testing.

The Role of Internet of Things (IoT) in Healthcare

IoT denotes the ability of everyday objects to access the internet and transmit and/or receive data [114]. IoT is an expansion of the conventional internet with the vast potential to provide interconnection between people, processes, software, actuators, and sensors [115]. This encompasses a wide range of internet-connected medical devices such as heart monitoring implants and infusion pumps, insulin pumps, and cochlear implants as shown in Fig. 10, with some of these devices generally used to detect, monitor, and manage people's health status and used in hospitals to deliver a preprogrammed level of fluids to patients [116]. These devices are intended to collect data from patients and integrate measurements into electronic health records. In summary, IoT is considered an all-powerful "intelligent connection of things." Several technologies such as edge computing, fog computing (FC), big data (BD) analytics, sensor technologies, and data science technologies fused to bring the term "Internet of Things" [115]. IoT advancement has called for its deployment in many fields [117]. Wearable devices can generate data which are synced with another devices for data analysis and history [116]. The healthcare industry has been transformed by services by supplying solutions to diverse healthcare problems. The widely used HIoT services are shown in Fig. 8.

Healthcare in summary is defined as taking preventive or necessary procedures to improve a person's well-being [115]. This can be accomplished through surgery, medication administration, or lifestyle changes. These services are often provided by a healthcare system that is composed mostly of hospitals and physicians. IoT offers many benefits, including monitoring patients more closely and using data for analytics. Home healthcare can provide substantial benefits to patients in terms of a higher quality of life, improved outcomes, and reduced healthcare costs. Also, patients who receive care at home may find it more enjoyable because they are in a familiar and convenient environment.

Patients are responsible for disclosing accurate and comprehensive information about their current and past medical conditions and must notify the authorized caregiver of any changes to their overall health status. Healthcare providers have a duty to notify or educate patients about their health, provide pertinent information on illnesses and

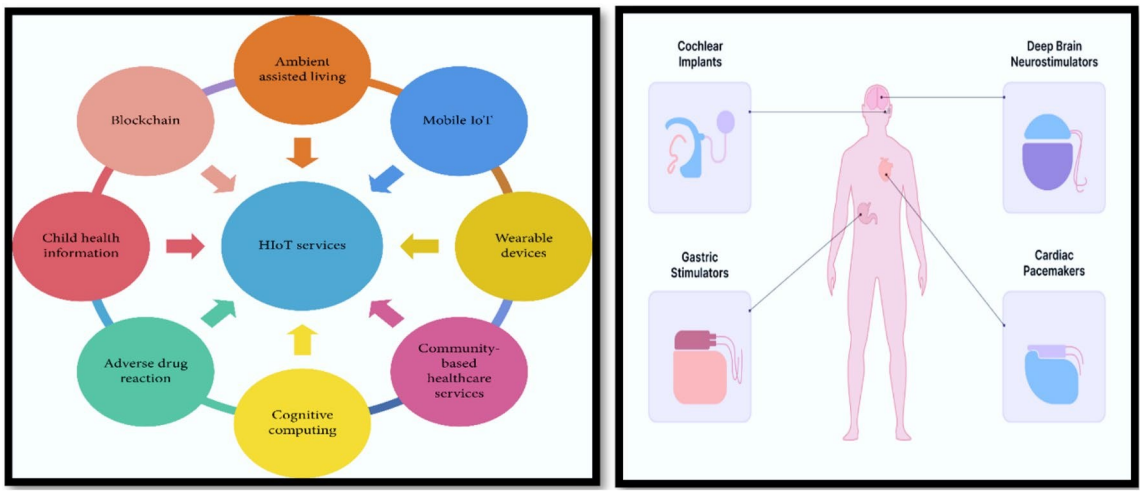

Fig. 8 Widely used HIoT services and examples of medical services [117]

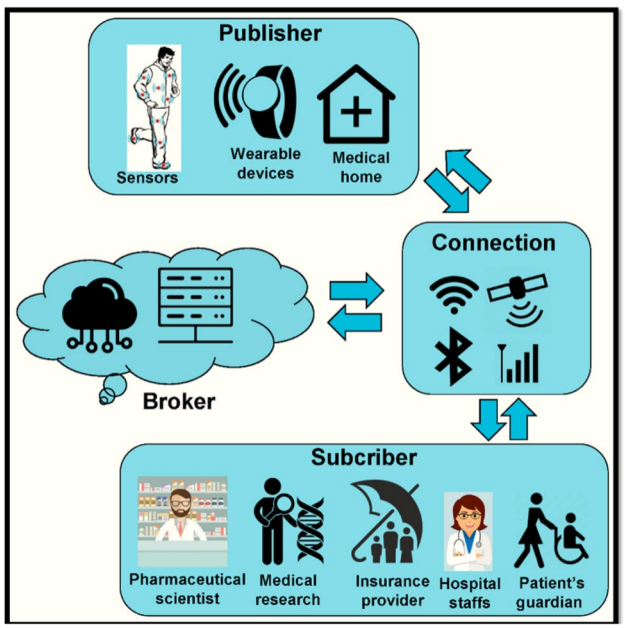

Fig. 9 Architecture of an HIoT framework [118]. @ Creative Commons License

treatments through counseling, and give appropriate advice when necessary. They can also help in diagnosing and treating illnesses based on the symptoms that are present using applicable standards [119]. There are several areas in healthcare where IoT is playing an important role. These include "Eldercare," which entails tracking elderly residents or patient's movements at nursing homes, and hospitals to provide effective medical care. Figure 9 illustrates the architecture of an HIoT framework. The FDA has already established universal device identifiers for medical devices in IoT applications. By this, there is tagging of the metadata generated by connected devices that would allow data to be closely tracked as it travels between devices or between devices and networks. However, the biggest challenge is devices' interoperability, which can lead to a network being exposed to new security vulnerabilities and additional risk. The rise in hackable medical devices has compelled the FDA to issue formal guidance on how medical device manufacturers should manage cyber vulnerability reports. The increase of intellectual property (IP)-connected sensors in hospital equipment and patients allows elimination of unnecessary waste and saves lives. IoT healthcare in an era of continuous growth, faces challenges, such as the collection, quality estimation, interpretation, and harmonization of the data that is derived from the vast amounts of heterogeneous IoT medical devices. A mechanism is produced to effectively address the intersection of these challenges. Through this mechanism, the collection of the different devices' datasets occurs, followed by the cleaning of the data. With connectivity, care can be delivered anywhere, lowering costs, and improving the patient's experience. Through IoT technologies, tens of billions of devices are expected to be connected to networks in near future [120–122].

Medical Device Software (MDS)

Software has been incorporated extensively into digital platforms serving both medical and non-medical purposes. Three (3) types of software are related to medical devices. These are Software as a Medical Device (SaMD), Software in a medical device (SiMD) and Software used in the manufacture or maintenance of a medical device [123]. All Software functions that are device functions are referred to as "device software functions" by the FDA [124]. Device

software functions comprise both "Software as a Medical Device (SaMD)" and "Software in a Medical Device (SiMD) [123]. A software function that satisfies the definition of a device and is implemented on a mobile platform is referred to as a "mobile medical app." Software used as a medical device can be anything from CAD software that executes image post-processing for breast cancer detection to software that permits a smartphone to examine the images obtained from a device using MRI for diagnostic purposes. The US FDA currently regulates software platforms used in healthcare on an intent-based classification, i.e., whether a software platform is intended to diagnose or treat disease or to affect the structure or function of the human anatomy or physiology [124]. Software platforms that meet the FDA's definition of a medical device are subsequently classified along the regulatory continuum (Class I, II, or III) and must follow appropriate FDA approval guidelines (via the 510(k), PMA, or De Novo pathways). Industry, international regulators, and healthcare professionals traditionally described such software as "standalone software" or "medical device software."

The FDA's Focus on Digital Health

Most medical devices connect to and transmit with other devices. Devices that have been approved or cleared by the FDA are being revised to incorporate digital elements. The FDA has defined several categories of medical device software considered as digital health technologies as shown in Table 3, with varying complexity and enforcement guidelines.

A thorough review of each category of digital health technologies is further provided in the subsequent sections. These digital health technologies have the potential to significantly advance individual patient care by enhancing the accurate diagnosis and treatment of disease. Further the benefits and the challenges of software medical device were also discussed in terms of the patience care improvement and the regulatory issues, respectively.

Software as a Medical Device (SaMD) by the FDA

In the modern healthcare industry, a huge role in providing medical services is given to diverse devices ranging from simple thermometers to complex machines like MRI or CT. But the increased interest in integrating technology with healthcare has led to the need for special software that can take over some functions of traditional medical equipment. Software was categorized as a medical device in a 2007 Global Organization Medical Device Directive. The International Medical Device Regulators Forum (IMDRF) is a worldwide group of medical device regulators that agreed on medical device regulations and has the FDA as chair of the working group. The IMDRF defined SaMD as software designed to be used for one or more medical purposes that achieve its goals without being a part of the hardware of a medical device [126]. Examples of SaMD include software that regulates the functioning of an installed medical device like a pacemaker and software that acts as diagnostic tools [127]. For instance, RAPID v 6.5 by Given Imaging Ltd is a software that utilizes patient-provided or device-collected data to generate 3D models for diagnosing medical conditions such as diabetes, heart disease, pneumonia, tumors, or breast cancer. This software leverages data from glucometers to calculate appropriate insulin dosages, eliminating the need for invasive procedures or additional radiation exposure

Table 3 Categories of digital health technologies (US FDA), Adopted from [125]

Category	Definition or Use	Example
Software as a Medical Device	Used for medical purposes	A microphone that detects interrupted breathing during sleep
Wireless	Uses wireless communication	Wi-Fi, Bluetooth
Artificial Intelligence	Initiates intelligent behavior and human learning	Uses algorithms for diagnostic information
Cybersecurity	Prevents unauthorized access or misuse of medical device	User authentication, biometrics, password
Mobile Medical Applications (MMAs)	Transforms mobile platform into regulated medical device	Sensors, display screens, attachments
Medical Device Data Systems (MDDS)	Electronic transfer, storage, or display of medical data	Collects medical data and transmits it to the data repository
Interoperability	Exchanges info through an electronic interface	Infusion pump to receive patient data & change its settings
Advanced Analytics	Uses large datasets to analyze patterns for medical purposes	Analyzes patient data and develop a treatment plan
Cloud	Internet-based data with a shared pool of resources that are shared on demand	Colposcope that stores images to be shared with doctor's ofice

from methods like MR or X-rays. Software applications that utilize microphones to identify the interrupted breathing patterns or analyze the physiological signals during sleep are all SaMD [128]. Through the microphone or camera of a smartphone, SaMD can assess sleep quality by determining sleep stages, recording snoring measurements including the identification of obstructive sleep apnea [129, 130]. Another example of SaMD involves software that aggregates data from multiple sources such as wearable devices, enabling healthcare professionals to remotely monitor real-time data, including heart rate, blood pressure, and other vital statistics.

SaMD in Wearable Devices for Safety Monitoring

Workplaces, including healthcare centers, are accompanied by inherent distractions, risks, and hazards. It is crucial to promptly identify and address the potential risk factors to ensure the safety, health, and productivity of workers. To support and enhance total worker health, intelligent hardware and software tools have emerged for identifying, mitigating, replacing, and controlling occupational hazards. Wearable devices enable continuous monitoring of individual workers and their surrounding environment, while connected software provides contextual information and decision-making support [131]. Workplace wearables, which encompass smart on-body accessories and personal protective equipment (PPE), track the activities, behavior, and physical condition of individual workers. Conversely, connected software, involving intelligent computing, data analytics, and storage platforms, serves as a central hub for extracting contextual information from distributed networks of workplace wearables. Currently, workplace technologies, which include both wearables and connected software, have specific applications. They are employed to detect factors such as awkward work postures, forceful exertions, vibrations, physical fatigue, mental acuity, stress levels, safety compliance, and the need for rest breaks [132, 133]. By creating smart and software-connected workplaces, which involve human-in-a-loop models, workers are equipped with improved situational awareness and remote supervision. Figure 10 illustrates the diverse shapes of wearable devices designed for health monitoring.

The 2016 21st-Century Cures Act (21CCA) additionally with guidance documents, public statements, and workshops from the FDA has urged policymakers and regulators to hasten efforts to clarify the policies for software-driven medical devices and innovation assistance. According to the intended usage and severity of the targeted medical condition, the IMDRF and FDA further risk-stratified SaMD platforms into four groups (I–IV), as shown in Table 4. The significance of this information given by SaMD is to inform healthcare choice. I, II, III, and IV are based on the levels of impact on

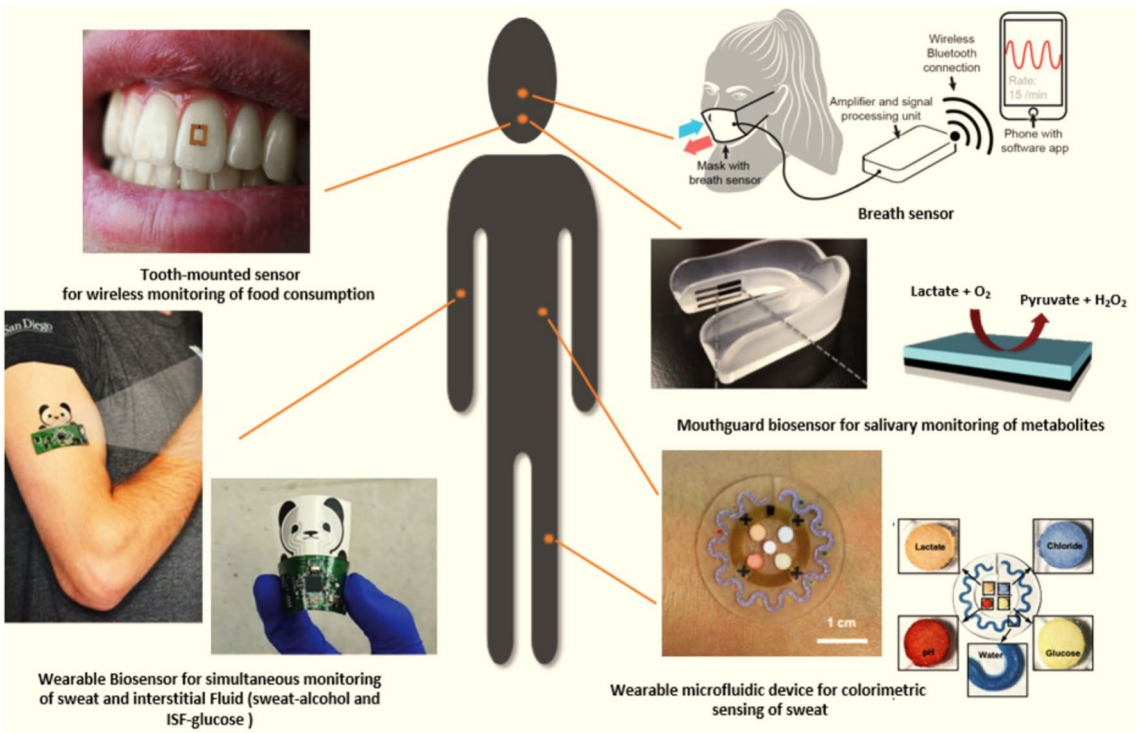

Fig. 10 Different shapes of wearable devices for health monitoring (tooth-mounted sensor photo courtesy of Mike Silver, SilkLab, Tufts University, October 23, 2019 (reprinted with permission from [134–138]

Table 4 Risk-stratified classification of SaMD platforms

Health condition	Diagnose/cure	Clinical management drive	Notify clinical management
Critical	IV	III	II
Serious	III	II	I
Non-serious	II	I	I

the patient. Category IV has the highest level of impact, and Category I has the lowest level of impact. With a preference for SaMD platforms that treat or diagnose severe and critical disorders as well as applications that drive clinical management of critical conditions, the FDA conducts independent reviews based on risk category.

Wireless Medical Device

Wireless medical devices function utilizing wireless radio frequency (RF) communication such as Wi-Fi, Bluetooth, and cellular/mobile phone to support healthcare delivery [139]. Monitoring patients remotely, controlling and programming a medical device, and transferring patient data from the medical device to another platform are examples of functions that employ wireless technology. Technology is increasingly incorporated into the design of medical devices as RF wireless technology keeps evolving. Other technological benefits include increasing patient mobility by eradicating wires that tether a patient to a medical bed providing healthcare professionals the capacity to remotely program devices and allowing physicians to remotely access and monitor patient data irrespective of the location. By providing doctors with real-time patient data without requiring them to visit the hospital in person and enabling real-time treatment modification, these advantages can have a significant impact on patient outcomes. To detect changes early and prevent more harmful effects from occurring, remote monitoring can also benefit certain populations, such as the elderly, by enabling home monitoring of chronic conditions [140].

Artificial Intelligence/Machine Learning-Based Medical Devices

Artificial intelligence (AI) began with the invention of *robota,* a word derived from the Czech meaning biosynthetic machines used as forced labor [140]. In 1955, John McCarthy coined the term "artificial intelligence," defining it as the science and engineering of developing intelligent machines into brilliant computer programs [141]. AI techniques in medical applications have three major categories, machine learning (ML) methods, deep learning, and natural language processing (NLP) [142]. The ML technique evaluates structured data like imaging, genetics, and electrophysiological data and helps assemble patients' characteristics or predict the prospect of the disease [143]. Deep learning is a more advanced form of ML technique used for more sophisticated data obtained from a medical dataset. The NLP method converts unstructured data, such as clinical data, into structured medical data. The NLP technique aims to convert texts into machine-readable structured data, analyzed by the ML technique [144]. A growing number of medical devices now have software that uses AI, particularly ML adopting the support vector machine (SVM) technique in ophthalmology and image processing. The Digital Health Center of Excellence at the Center for Devices and Radiological Health (CDRH) declared the artificial intelligence/machine learning (AI/ML)-based medical device software in their action plan [145]. One of the ML's most significant potential advantages is its capability to generate and extract significant insights from enormous amounts of data accumulated [146–151] daily while providing healthcare.

Advancements in consumer technologies, such as 3D bioprinting, cloud computing, AI, and blockchain, have translated to applications in the healthcare sector and require new regulatory guidelines that evolve with the rapidly changing technology. ML has the potential to improve healthcare systems around the world by optimizing hospital workflows, providing more accurate disease diagnoses, and providing patients with better medical treatment plans [71]. A summary of the role of AI in cardiovascular medicine is illustrated in Fig. 11. Some AI/ML autonomous devices have already been approved for sale in the US, such as IDX-DR, which was approved by the FDA in 2018 and is the first AI/ML diagnostic to offer a screening decision for eye condition diabetic retinopathy.

AI Application in Capsule Endoscopy

Endoscopy is the medical procedure used to directly visualize the inside of the gastrointestinal (GI) tract for potential disorders or diseases such as bleeding, ulcers, colon polyps, chronic refractory constipation, Crohn's disease, and Celiac disease [152, 153]. Conventional endoscopy utilizes a camera with an elongated flexible cable to enable imaging of various parts of the GI tract, such as the esophagus, gut, colon, and lower part of the small bowel. This process is time-consuming, uncomfortable, and painful for the patient and can solely be conducted by a qualified medical practitioner. Given Imaging developed a family of PillCam ingestible capsules for various purposes: SB series for the visualization of the small bowel mucosa, COLON series for the colon, and ESO series for the esophageal mucosa [154]. This innovative device was developed to address the limitations associated with conventional wired endoscopy.

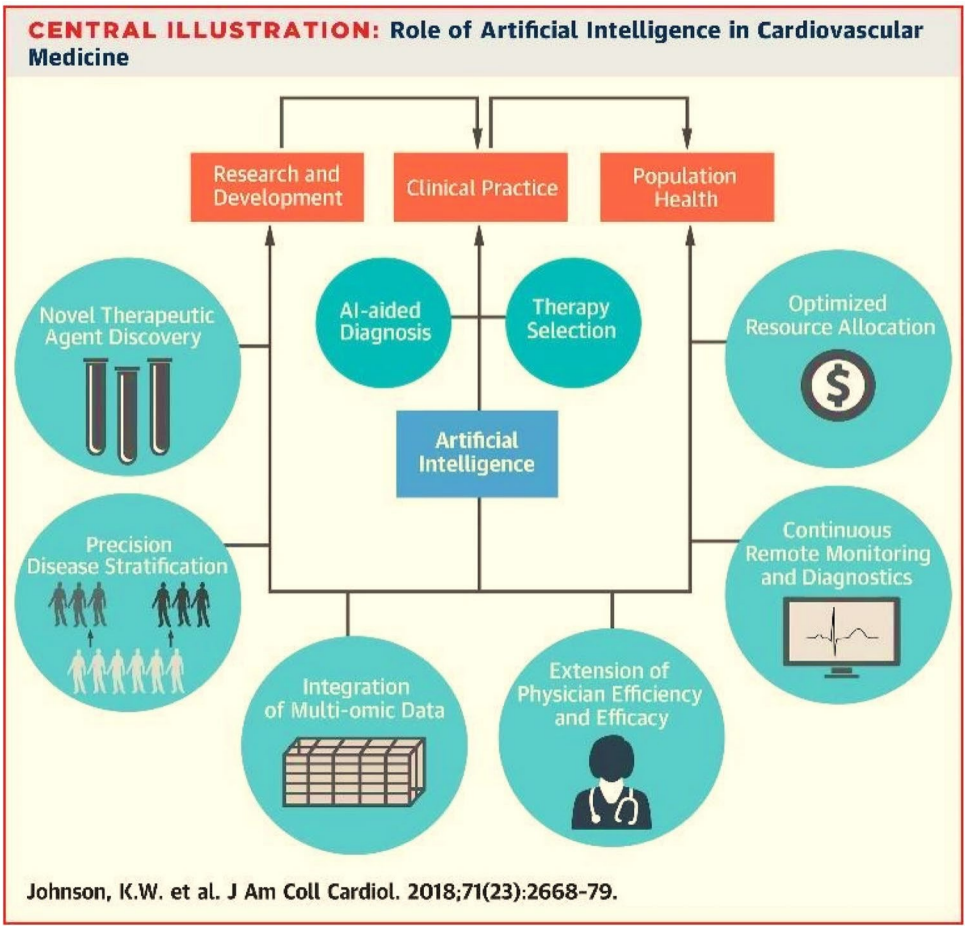

Fig. 11 Role of AI in cardiovascular medicine [151]

The procedure for examining the gastrointestinal (GI) tract using this wireless camera is commonly referred to as wireless capsule endoscopy (WCE) or capsule endoscopy (CE) [155, 156]. Studies have demonstrated that this approach has a diagnostic yield of approximately 60–70% and is particularly effective in identifying sources of bleeding that may go unnoticed with other methods [157, 158]. Some of the commercially available ingestible capsules include M2A (i.e., mouth-to-anus), PillCam SB, PillCam SB 2, and Endo capsules as shown in Fig. 12. Despite technological advancements in endoscopy, gastroenterologists manually review WCE video to identify GI tract issues [159, 160]. Manual reviewing is time-consuming and costly, and it frequently requires the doctor's full attention [160] due to concerns with interpatient variability and disease complexity [161]. Due to human limitations, this method is more susceptible to diagnostic mistakes. Also, due to mechanical restrictions and the capsule endoscopes' short depths, capsule endoscopes only record limited images with low lighting and limited power as well as videos with low resolutions and low frame rates transmitted wirelessly to a recorder. This increases the likelihood that lesions will be missed or the bowel cleansing score won't be recorded [162].

Utilizing computational methods in post-procedural management has the potential to enhance the quality of captured images and reduce the image review time and error rates significantly. The advancement of computer vision technology has the capacity to improve the diagnostic limitations of capsule endoscopy (CE) [164]. AI appears to be a useful technology that could enhance CE's performance measures, which would ultimately result in better patient care. The introduction of AI, particularly deep learning, into computer vision has shown remarkable advancements in lesion recognition [165–167]. AI brings several benefits to the diagnosis of capsule endoscopy (CE), including improved time eficiency [167, 168]. For instance, the human reading of an entire small bowel CE video typically takes between 30 and 90 min. In contrast, AI algorithms are significantly faster, capable of analyzing a complete CE video in under 30 min and sometimes even less than 10 min [169, 170]. AI also contributes to the reduction of errors by minimizing human limitations such as biases, fatigue, or lack of experience. AI technology enhances training and learning opportunities by selectively providing clinicians with abnormal CE images for review. Modern ingestible capsules can be enhanced with a variety of cutting-edge features such as microrobotics,

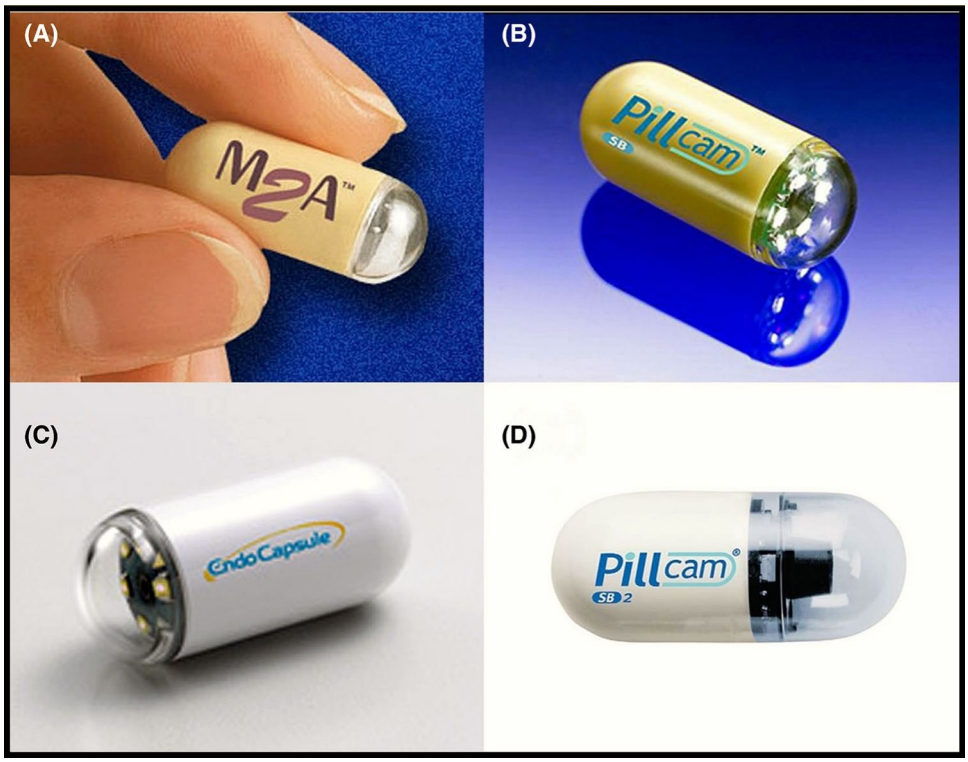

Fig. 12 Capsule endoscopies for small bowel before 2012. **A** M2A (Given Imaging Ltd). **B** PillCam SB (Given Imaging Ltd). **C** EndoCapsule (Olympus Corporation). **D** PillCam SB 2 (Given Imaging Ltd). Copyright from [163]

panoramic imaging, controlled sampling, and delivery and rapid reading software's to support diagnostic and therapeutic purposes [171–173].

FDA Guidelines for Ingestible Wireless Telemetric Capsules

The FDA reclassified ingestible capsule wireless gastrointestinal imaging system from class III to Class II and the first capsule model for the small intestine was approved by the FDA in 2001 [173]. Also, the SmartPill was the first wireless capsule technology with sensors for pH, core body temperature, and pressure to receive FDA approval in 2003 [162]. Ingestible capsules utilize different methods for movement such as electrical stimulation, magnetic actuation, robotic manipulators, or specialized placement devices within the GIT. These approaches are developed primarily for individuals who are candidates for video capsule endoscopy but face challenges in swallowing or passing the capsule through the pylorus. Manufacturers of ingestible capsules are required to submit a Premarket Notification 510(k), demonstrating that the device is substantially equivalent to an already legally distributed product in the United States. The FDA Class II Special Controls Guidance provides instructions on gathering clinical information concerning various aspects, including capsule ingestion ease, intestinal transit time, diagnostic yield, adverse events, and consensus among reviewers regarding image interpretation [173]. Patient labeling for ingestible capsules should contain instructions on proper operation, monitoring, maintenance, reporting, as well as information about associated risks and benefits. This labeling should include details about dietary restrictions, limitations on physical activity, safety features, usage limits, possible symptoms (such as nausea, pain, or vomiting), warnings, precautions, contraindications, and potential electromagnetic interference [173]. The FDA emphasizes a least burdensome approach for device manufacturers to comply with its guidance and address identified issues to facilitate smooth licensing and approval. The above mentioned capsule devices undergo rigorous evaluation for various factors, including biocompatibility, electrical and mechanical safety, functional reliability (such as structural integrity and image acquisition), prevention of intestinal obstruction or injury, avoidance of misinterpretation of captured images, RF radiated power, and electromagnetic compatibility (EMC), which involves mitigating interference with other medical devices as well as within the device itself (e.g., interference with image acquisition) to gain acceptance from FDA.

The First-Approved FDA AI-Medical Device for the Diagnosis of Diabetic Retinopathy

Diabetic retinopathy (DR) is the major cause of diabetes and has been proven to be the leading cause of blindness and other vision impairment among working-age adults. DR begins to develop when high blood sugar levels harm the blood vessels of the retina. Early detection of retinopathy is

crucial in managing care for the millions of people with diabetes, thus the FDA approved the first AI-medical device for the diagnosis of diabetic retinopathy [174]. Currently, about 350 AI/ML-based medical devices have been approved by the FDA. The first device to be approved by the FDA is the diabetic retinopathy detection device mostly abbreviated as IDx-DR. The FDA approved the marketing of the first medical device to use AI to detect diabetic retinopathy (including macular edema) in adults who have diabetes. Among individuals living with diabetes, the prevalence of diabetic retinopathy is approximately 28.5% in the United States [175].

IDx-DR provides a screening decision without requiring a clinician to interpret the image or results, allowing it to be used by healthcare providers who are not typically involved in eye care. In IDx-DR device, using a fundus camera, the trained operator captures two images per patient's eye. These images are fed into the IDx-DR, which analyzes them for signs of diabetic retinopathy (including macular edema) and returns results in under 30 s. The patient will have to retest in 12 months with a negative result. However, if a disease is detected, the patient is referred to an eye care professional. Figure 13 summarizes how IDx-DR works. Nine hundred patients were evaluated with diabetes data from ten primary care sites in a clinical study of retinal images to confirm the significance of the AI/ML device. The study's goal was to determine how frequently IDx-DR could correctly detect patients with more than mild DR. IDx-DR correctly identified the presence of more than mild diabetic retinopathy in 87.4% of the patients in the study.

Cybersecurity Implications Associated with AI/ML-Based SaMD

All medical devices carry some element of risk, as evidenced by the FDA's risk-based framework for approval. Because software-driven devices update at frequent intervals, each update has the potential to introduce new flaws and thus increase risks for patients. Medical devices built with networking capabilities have increased and although this can be functionally important for devices' remote monitoring and control, it represents significant cybersecurity risks by creating new attack surfaces and vulnerabilities that don't seem to be present in isolated devices. This risk was identified in 2015, when the FDA and the Industrial Control Systems Cyber Emergency Response Team issued an alert about a Hospira Symbiq infusion system that could give an attacker access to remotely control the device, potentially altering medication administration. Similarly, in August 2017, the FDA recalled a series of implantable cardiac defibrillators produced by Abbott (formerly St. Jude

Fig. 13 **A** A fundus camera used to take images [176]. **B** The IDx-DR which processes the images and gives an output [177]. **C** The diabetic retinopathy possible results [178]. **D** The IDx-DR device with a brown eye and imaged eye [179]

Medical) that potentially allowed an attacker to switch pacemaker commands remotely. Another product safety unique to SdMDs is software reliance on third-party components. SdMDs may contain off-the-shelf (OTS) components that the device's manufacturer did not create. This addition raises liability and responsibility for the manufacturer and the original software distributor. Although hardware medical devices may use components from another manufacturer, the difference with software-driven devices is that, as a results of large-scale updates, software problems are introduced later by the OTS software distributor, impacting the whole population of existing device users. Another significant risk to product safety and security in SdMDs is their longevity and transparency of software. Situations where the software manufacturer goes out of business, the corporate may lose the ability to care for, manage, and support the SdMD. As a result of natural business cycles in medical technology companies, there could presumably be a gradual increase within the number of devices in circulation that depend upon software that is not supported or updated. As clinical guidelines change and as new security vulnerabilities are discovered, this gap is probably going to represent a growing product safety issue.

Medical AI/ML also introduces new challenges for society and current regulators such as the FDA. Questions such as “Which medical AI/ML-based products should be subjected to regulatory scrutiny?” “What evidence should regulators require manufacturers of AI/ML-based SaMD to submit as a condition for marketing?” and “How can improvements be made to ensure AI/ML-based SaMD’s performance in real time while also safeguarding their safety and effectiveness?” [71] are all potential questions in demand in software operations. The current AI/ML-based SaMDs that have obtained FDA marketing authorization have "locked" algorithms, as they do not evolve and do not use new data to improve their performance (FDA). If the algorithm changes because of its use, such SaMD will most likely require another FDA round of review (FDA). While government regulation in the United States is less stringent, cases like Cambridge Analytica/Facebook should remind the government that actions must be taken, and company behavior must change. The insurance Portability and Accountability Act (HIPAA) may be a compliance focus for health information concerns [180]. This act elaborates upon rules requiring, among other things, the formulation of policies and the setup of coaching systems for those with access to sensitive data [180]. Moreover, HIPAA does not hinder the action of individual states, where it further protects the individual’s right to privacy. Figure 14 shows the US regulatory framework. Therefore, within the last decade, personal data regulation and privacy concerns are growing. Implementing deep learning systems will thus necessitate rethinking confidentiality and other core tenets of medical ethics. Data protection cannot depend on current technologies that allow the spreading of non-public data and necessitates data sharing at an outsized and uncontrolled scale. Deep learning should be used by AI-medical devices in radiology and medicine in general to generate data about patients without requiring personally identifiable information in return.

Mobile Medical Applications

Mobile Medical Applications (MMAs) could be a “mobile app that meets the definition of a medical device in section 201(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and meant to be used either as an adjunct to a regulated medical device or to remodel a mobile platform into a regulated medical device. Just as SaMDs, MMAs as medical devices are defined by their intended use, as illustrated by the labeling claims, advertising materials, and

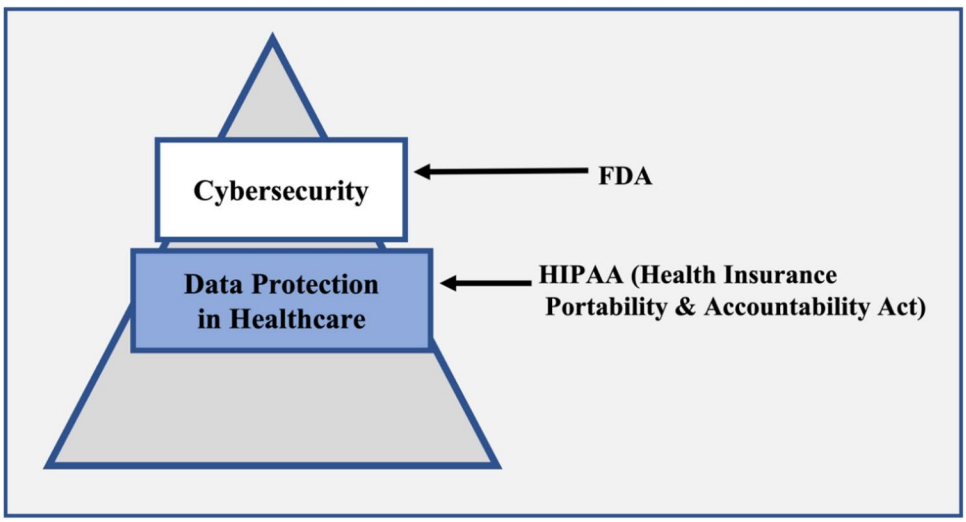

Fig. 14 Regulatory framework in the US on data protection

written or oral statements by manufacturers. Supported by the 2015 guidance documentation, the FDA regulates only those MMAs that act as medical devices (as defined above) and "whose functionality may pose a risk to a patient's safety if the mobile app weren't to function as intended" [181]. Like hardware devices, MMAs are often categorized as Class I, II, or III and, as a result, would require general controls, 510(k), or PMA, respectively, for clearance. Given the recent growth of mobile medical technologies, the FDA focuses its regulatory sights on a subset of applications that transform a mobile platform into a regulated medical device. Medical Mobile apps that do not function as medical devices include apps used as medical textbooks or other reference material, apps used for general patient education and those that facilitate general office operations.

Medical Device Data Systems

Medical Device Data Systems (MDDS) are platforms that provide electronic transfer or storage of medical data, conversion of medical data type, or electronic display of medical data (FDA). In 2011, the FDA reclassified all MDDS as class I (low risk) medical devices, stating that general controls like Quality System Regulations would offer reasonable assurance of safety and efficacy for this category of medical software. A MDDS does not revise the data or revise the display of the data, and it does not by itself regulate the functions or parameters of any other medical device. MDDS may or may not be intended for active patient monitoring. Non-Device-MDDS include software functions that store patient data, such as blood pressure readings, for review at a later time; convert digital data generated by a pulse oximeter into a format that can be printed; and display a previously stored ECG for a particular patient [182].

Clinical Decision Support Software

The last software medical device categorized by the FDA includes Clinical Decision Support Software such as advanced analytics, cloud, and interoperability. Advanced analytics utilizes analytical and statistical modeling techniques to analyze large amounts of patient datasets and provides personalized recommendations in terms of diagnosis and treatment plans. SaMD can make use of cloud computing software and data storage resources to analyze the data and store the patient-specific datasets for future review. Mobile medical devices or medical devices, such as an infusion pump, and centralized monitoring system can be used to receive the data and perform appropriate action commands based on the patient's condition. Due to the 21st-Century Cures Act, CDSS platforms were excluded as medical devices as illustrated in Table 5.

CDSS platforms that don't give independent review by a healthcare provider could be regulated by the FDA as a medical device, requiring it to obtain standard regulatory clearance before going to market. The FDA has also issued guidance on using OTS software in medical devices. This concerns explicitly products that utilize a standard software package, like Windows or macOS, which runs a proprietary medical software application. "A basic set of need-to-document items is usually recommended for all OTS software, and a close discussion is provided on additional (special) needs and responsibilities of the manufacturer when the severity of the hazards from OTS software failure becomes more significant," according to the FDA.

Benefits of Software Medical Device

Software has safety improvements. Software can be streamlined eficiently and distributed extensively. The safety recall of a cardiac stent might bear a major procedure at a high cost to regulators, manufacturers, and healthcare providers but software updates require accessibility and, in some cases, can be delivered automatically. The FDA has issued guidance about remote software updates (FDA), and inventors have begun enforcing these updates in specific bias, similar to insulin pumps [183]. Software holds great promise for the robotization of safety reporting for post-market surveillance, allowing merchandisers and controllers more streamlined access to safe data for a device. It can induce edge and savings in processes that calculate on cost registries and large-scale reporting systems [184]. Furthermore, modern software development processes often use continuous integration-and-delivery methodologies, an example is

Table 5 Software functionalities of CDSS excluded as medical devices

CDSS functionalities excluded as medical device
When functionality is not intended to amass, process, or analyze a medical image or a proof from an in vitro diagnostic device or a pattern or signal from an indication acquisition system
When it is meant to display, analyze, or print medical information for a few patients or other medical information
When it is intended to assist or make recommendations to a healthcare professional regarding disease or condition prevention, diagnosis, or treatment;
Designed to give the healthcare professional the ability to independently review the recommendations that the software suggests

the dissemination of latest software components whenever major new functionalities become available. This improvement offers tremendous advantages for patients; for instance, the incorporation of a re-trained algorithm will be quick because it is readily accessible.

Challenges of Software Medical Device (Software-Specific Regulatory Issues)

After a product's launch, software is predicted to be regularly updated, modified, and maintained. This software feature necessitates a more dynamic regulatory approach to account for meaningful changes during a product's lifecycle. Balancing the necessity for agility and tight regulation is challenging in practice. The regulator's role will have to transcend post-market inspections and surveillance to incorporate more complex monitoring and testing. The distribution of software dynamic medical devices (SdMDs) is another challenge. Hardware medical devices are available for distribution through the formal healthcare system (that is, in hospitals, pharmacies, and physicians' ofices). Software distribution, however, can and typically does occur outside traditional medical supply chains. It is dificult for a patient within the US to access a hardware device favorably just for marketing outside the country but can be straightforward for them to download software that has approval to be used abroad. Software may be hardware dependent or agnostic. The identical wares could also be run on multiple devices with designs made by different hardware developers (for example, software for digital image display on radiology devices may have licenses to multiple manufacturers). From a regulatory standpoint, this might raise questions of accountability; if a mistake arises, it's going to be unclear whether the fault lies with the software component, the hardware component, or the interaction between the two.

Conclusion

This review article provides an in-depth analysis of the existing classifications of hardware and software medical devices along with their applications based on the FDA guidelines. A comprehensive understanding of the regulatory approval pathway for biomedical device development is presented. Emphasis is placed on the significance of human factors engineering while developing biomedical devices to minimize the risk of product recalls, use errors, and encourage safe usage. Emerging topics including the IoT, software as medical devices, AI, ML, mobile medical devices, and clinical decision software support systems are discussed. An effective use of AI and ML tools would advance the development of biomedical devices. On the contrary, an unethical use of this cutting-edge technology could be threatening to patients, physicians (radiologists), and regulatory authorities. Challenges such as the new policy on data protection and cybersecurity regulation, the controversy about bizarre accountability and responsibility issues, and the questions on the fiduciary relationship between patients and AI-medical systems will need to be addressed. Developing cyber security policies and regulations can aid in addressing these challenges by providing privacy protection, security, and ethical use of delicate information to ensure the safety of both humans and machines. Transitioning from a product approach to a systems approach whereby product designers, manufacturers, early clinical trials, regulators, patients, and users are wholly considered prior to making regulatory decisions can tackle major challenges in biomedical device development. Early clinical trials and device development policies should be refined, and new policies should be established to address the current challenges. Lastly, this review paper elucidates the future trends in biomedical device development and their potential implications for patient care. By offering a comprehensive understanding of the present landscape and future prospects, this review article contributes to the continuous efforts aimed at enhancing the safety, effectiveness, and overall impact of biomedical devices on healthcare outcomes [146, 158, 168].

Acknowledgements The authors acknowledge the funding from the National Science Foundation (NSF) #1663128, #2100739, #2100850, #2200538. We would like to thank the Center of Excellence in Product Design and Advanced Manufacturing (CEPDAM), North Carolina A & T State University.

Author Contributions All authors contributed to the composition of the manuscript. The final version of the manuscript has been approved by all authors.

Funding The authors acknowledge the funding from the National Science Foundation (NSF) #1663128, #2100739, #2100850, #2200538.

Data Availability Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

Competing interests There are no competing interests for this review article.

Ethical Approval All the information presented is cited appropriately and relevant literature in support of the claims made.

References

1. U.S. Food and Drugs Administration, Importing Medical Devices (2018), https://www.fda.gov/industry/importing-fda-regulated-products/importing-medical-devices#What is a medical device.
2. World Health Organization, Medical Devices. https://www.who.int/health-topics/medical-devices#tab=tab_1

3. C. Peña, K. Li, R. Felten, N. Ogden, M. Melkerson, An example of US Food and Drug Administration device regulation: medical devices indicated for use in acute ischemic stroke. Stroke **38**(6), 1988–1992 (2007)
4. S.K. Gupta, Medical device regulations: a current perspective. J. Young Pharm. **8**(1), 6 (2016)
5. S. Desai, S. Parupelli, Additive manufacturing (3D printing), in *Maynard's Industrial and Systems Engineering Handbook*, 6th ed. (Springer, Berlin, 2022)
6. S. Bose, S.F. Robertson, A. Bandyopadhyay, Surface modification of biomaterials and biomedical devices using additive manufacturing. Acta Biomater. **66**, 6–22 (2018)
7. M. Olowe, S.K. Parupelli, S. Desai, A review of 3D-printing of microneedles. Pharmaceutics **14**(12), 2693 (2022)
8. E. Adarkwa, R. Kotoka, S. Desai, 3D printing of polymeric coatings on AZ31 Mg alloy substrate for corrosion protection of biomedical implants. Med. Devices Sensors **4**(1), e10167 (2021)
9. G. Haeberle, S. Desai, Additive manufacturing (3D printing) of thermoform tooling. Int. J. Mech. Prod. Eng **7**, 1–4 (2019)
10. A. Aljohani, S. Desai, 3D printing of porous scaffolds for medical applications. Am. J. Eng. Appl. Sci. **11**(3), 1076–1085 (2018)
11. S.K. Parupelli, S. Desai, Understanding hybrid additive manufacturing of functional devices. Am. J. Eng. Appl. Sci. **10**, 264–271 (2017). https://doi.org/10.3844/ajeassp.2017.264.271
12. F. Aldawood, S. Desai, Additive manufacturing of compensator devices for radiation therapy, in *Proceedings of the 2020 IISE Annual Conference* (2020)
13. J. McKenzie, S. Parupelli, D. Martin, S. Desai, Additive manufacturing of multiphase materials for electronics, in *IIE Annual Conference. Proceedings*, pp. 1133–1138 (2017)
14. L.J. Kelly, T. Jones, Medical device classification: focus on vascular access. Br. J. Nurs. **27**(14), S14–S19 (2018). https://doi.org/10.12968/bjon.2018.27.14.S14
15. Centre for Devices & Radiological Health. FDA, Unique device identification and the EHR-types of medical devices and examples (2013), https://slideplayer.com/slide/1480438/. Accessed 13 July 2022
16. U.S. Food and Drug Administration-Products and Medical Procedures (2021), https://www.fda.gov/medical-devices/products-and-medical-procedures
17. A.N. Johnson, Medical Devices & MedTech Products (2020), https://angelanjohnson.com/medicaldevices/
18. FDA, US Food and Drugs Administration-Classify Your Medical Device (2018), https://www.fda.gov/medical-devices/overview-device-regulation/classify-your-medical-device
19. US Food and Drug Administration (FDA), Consumers (Medical Device), *2017*. https://www.fda.gov/medical-devices/consumers-medical-devices/learn-if-medical-device-has-been-cleared-fda-marketing
20. A.V. Kaplan, D.S. Baim, J.J. Smith, D.A. Feigal, M. Simons, D. Jefferys, T.J. Fogarty, R.E. Kuntz, M.B. Leon, Medical device development: from prototype to regulatory approval. Circulation **109**, 3068–3072 (2004)
21. L.H. Monsein, Primer on medical device regulation. Part II. Regulation of medical devices by the US Food and Drug Administration. Radiology **205**, 10–18 (1997)
22. L. Keutzer, U.S.H. Simonsson, Medical device apps: an introduction to regulatory affairs for developers. JMIR mHealth uHealth **8**(6), e17567 (2020)
23. B. Zhang, S.B. Shankara, J. Guo, H. Zhang, Pivotal clinical trials with patient-reported outcome measures in premarket approval applications for high-risk medical devices from 2005 to 2018: review, examples, and regulatory considerations. Contemp. Clin. Trials **116**, 106757 (2022)
24. J. Li, M. Stachowski, Z. Zhang, Application of responsive polymers in implantable medical devices and biosensors, in *Switchable and Responsive Surfaces and Materials for Biomedical Applications* (Woodhead Publishing, Cambridge, 2015), pp. 259–298
25. R. Plowman et al., The rate and cost of hospital-acquired infections occurring in patients admitted to selected specialties of a district general hospital in England and the national burden imposed. J. Hosp. Infect. **47**(3), 198–209 (2001). https://doi.org/10.1053/jhin.2000.0881
26. E.E. Bennett, J. VanBuren, S.L. Bratton, Presence of invasive devices and risks of healthcare-associated infections and sepsis. J. Pediatr. Intensive Care **7**, 188–195 (2018)
27. N. Buetti et al., Strategies to prevent central line-associated bloodstream infections in acute-care hospitals: 2022 update. Infect. Control Hosp. Epidemiol. **43**(5), 553–569 (2022)
28. R.B. Wilson, Y. Farooque, Risks and prevention of surgical site infection after hernia mesh repair and the predictive utility of ACS-NSQIP. J. Gastrointest. Surg. **26**(4), 950–964 (2022)
29. R.J. Pratt et al., epic2: National evidence-based guidelines for preventing healthcare-associated infections in NHS hospitals in England. J. Hosp. Infect. **65**, S1–S59 (2007)
30. G. Flodgren, L.O. Conterno, A. Mayhew, O. Omar, C.R. Pereira, S. Shepperd, Interventions to improve professional adherence to guidelines for prevention of device-related infections. Cochrane Database Syst. Rev. (3), CD006559 (2013)
31. D. Lebeaux, J.-M. Ghigo, C. Beloin, Biofilm-related infections: bridging the gap between clinical management and fundamental aspects of recalcitrance toward antibiotics. Microbiol. Mol. Biol. Rev. **78**(3), 510–543 (2014)
32. L. Hall-Stoodley et al., Towards diagnostic guidelines for biofilm-associated infections. FEMS Immunol. Med. Microbiol. **65**(2), 127–145 (2012)
33. M.K. Kasliwal, L.A. Tan, V.C. Traynelis, Infection with spinal instrumentation: review of pathogenesis, diagnosis, prevention, and management. Surg. Neurol. Int. **4**(Suppl 5), S392 (2013)
34. L. Sangkum, G.L. Liu, L. Yu, H. Yan, A.D. Kaye, H. Liu, Minimally invasive or noninvasive cardiac output measurement: an update. J. Anesth. **30**(3), 461–480 (2016). https://doi.org/10.1007/s00540-016-2154-9
35. C. Lin, Y. Tsai, Y. Lu, J. Yang, M. Chen, Application of a novel biosensor for salivary conductivity in detecting chronic kidney disease. Biosensors **12**(3), 178 (2022). https://doi.org/10.3390/bios120301782022
36. W. Li, O. Auciello, R.N. Premnath, B. Kabius, Giant dielectric constant dominated by Maxwell–Wagner relaxation in Al_2O_3/TiO_2 nanolaminates synthesized by atomic layer deposition. Appl. Phys. Lett. **96**(16), 162907 (2010)
37. R. Magjarević, Non-invasive and minimally invasive medical devices. Report, May, pp. 10–12 (2017)
38. C.H. Chen, T.H. Tao, Y.H. Chou, Y.W. Chuang, T.B. Chen, Arteriovenous fistula flow dysfunction surveillance: early detection using pulse radar sensor and machine learning classification. Biosensors (2021). https://doi.org/10.3390/bios11090297
39. J.F. Mooney et al., Relative value of cystatin C and creatinine-based estimates of glomerular filtration rate in predicting long-term mortality after cardiac surgery: a cohort study. BMJ Open **9**(9), e029379 (2019)
40. T.K. Chen, D.H. Knicely, M.E. Grams, Chronic kidney disease diagnosis and management: a review. JAMA **322**(13), 1294–1304 (2019). https://doi.org/10.1001/jama.2019.14745
41. K.P. Bhatia et al., Consensus statement on the classification of tremors from the task force on tremor of the International Parkinson and Movement Disorder Society. Mov. Disord. **33**(1), 75–87 (2018)
42. E.D. Louis, Tremor. Contin. Lifelong Learn. Neurol. **25**(4), 959–975 (2019)

43. V. Srinivasan, V.K. Pamula, M.G. Pollack, R.B. Fair, Clinical diagnostics on human whole blood, plasma, serum, urine, saliva, sweat, and tears on a digital microfluidic platform, in *Proc. MicroTAS*, pp. 1287–1290 (2003)
44. G. Gaobotse, E. Mbunge, J. Batani, B. Muchemwa, Non-invasive smart implants in healthcare: Redefining healthcare services delivery through sensors and emerging digital health technologies. Sensors Int. **3**, 100156 (2022). https://doi.org/10.1016/j.sintl.2022.100156
45. K. Dixit, S. Fardindoost, A. Ravishankara, N. Tasnim, M. Hoorfar, Exhaled breath analysis for diabetes diagnosis and monitoring: relevance, challenges and possibilities. Biosensors **11**(12), 476 (2021)
46. K. Lee et al., Real-world outcomes of glucose sensor use in type 1 diabetes—findings from a large UK centre. Biosensors **11**(11), 457 (2021)
47. Graphene patches over diabetes treatment (2016), https://www.sciencedirect.com/science/article/abs/pii/S1748013216301347?via%3Dihub
48. F.F. Franco, R.A. Hogg, L. Manjakkal, Cu_2O-based electrochemical biosensor for non-invasive and portable glucose detection. Biosensors (2022). https://doi.org/10.3390/bios12030174
49. J. Kim, A.S. Campbell, B.E.-F. de Avila, J. Wang, Wearable biosensors for healthcare monitoring. Nat. Biotechnol. **37**(4), 389–406 (2019)
50. R.J. Morrison et al., Regulatory considerations in the design and manufacturing of implantable 3D-printed medical devices. Clin. Transl. Sci. **8**(5), 594–600 (2015). https://doi.org/10.1111/cts.12315
51. E. Adarkwa, A. Roy, J. Ohodnicki, B. Lee, P.N. Kumta, S. Desai, 3D printing of drug-eluting bioactive multifunctional coatings for orthopedic applications. Int. J. Bioprinting **9**(2), 661 (2023)
52. S.K. Parupelli, S. Desai, Hybrid additive manufacturing (3D printing) and characterization of functionally gradient materials via in situ laser curing. Int. J. Adv. Manuf. Technol. **110**, 543–556 (2020)
53. F.K. Aldawood, S.X. Chang, S. Desai, Design and manufacture of a high precision personalized electron bolus device for radiation therapy. Med. Devices Sensors **3**(6), e10077 (2020)
54. G. Haeberle, S. Desai, Investigating rapid thermoform tooling via additive manufacturing (3D printing). Am. J. Appl. Sci **16**, 238–243 (2019)
55. J. McKenzie, S. Desai, Investigating sintering mechanisms for additive manufacturing of conductive traces. Am. J. Eng. Appl. Sci. **11**(2), 652–662 (2018)
56. S. Desai, B. Bidanda, P.J. Bártolo, Emerging trends in the applications of metallic and ceramic biomaterials, in *Bio-Materials and Prototyping Applications in Medicine* (Springer, Cham, 2021), pp. 1–17
57. S. Desai, M.R. Shankar, Emerging trends in polymers, composites, and nano biomaterial applications, in *Bio-Materials and Prototyping Applications in Medicine* (Springer, Cham, 2021), pp. 19–34
58. S. Desai, P. Gomes, Design for nano/micro manufacturing using a flexible decision making technique (AHP). J. Udyog Pragati **39**(2), 18–25 (2015)
59. J. Perkins et al., Direct writing of polymeric coatings on magnesium alloy for tracheal stent applications. Ann. Biomed. Eng. **43**, 1158–1165 (2015)
60. S. Desai, B. Harrison, Direct-writing of biomedia for drug delivery and tissue regeneration, in *Printed Biomaterials: Novel Processing and Modeling Techniques for Medicine and Surgery*, pp. 71–89 (2010)
61. S. Desai, M.R. Shankar, Polymers, composites and nano biomaterials: current and future developments, in *Bio-Materials and Prototyping Applications in Medicine* (Springer, Cham, 2008), pp. 15–26
62. S. Desai, B. Bidanda, Metallic and ceramic biomaterials: current and future developments, in *Bio-Materials and Prototyping Applications in Medicine* (Springer, Cham, 2008), pp. 1–14
63. P. Honigmann, N. Sharma, B. Okolo, U. Popp, B. Msallem, F.M. Thieringer, Patient-specific surgical implants made of 3D printed PEEK: material, technology, and scope of surgical application. Biomed. Res. Int. **2018**, 4520636 (2018)
64. U.S. Food and Drugs Administration, Medical applications of 3D printing (2017), https://www.fda.gov/medical-devices/3d-printing-medical-devices/medical-applications-3d-printing
65. U.S. Food and Drugs Administration, Technical considerations for additive manufactured medical devices (2018), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-additive-manufactured-medical-devices
66. A.A. Raheem et al., A review on development of bio-inspired implants using 3D printing. Biomimetics **6**(4), 65 (2021)
67. A.L. Jardini et al., Improvement in cranioplasty: advanced prosthesis biomanufacturing. Procedia CIRP **49**, 203–208 (2016)
68. X. Chen, J.K. Possel, C. Wacongne, A.F. Van Ham, P.C. Klink, P.R. Roelfsema, 3D printing and modelling of customized implants and surgical guides for non-human primates. J. Neurosci. Methods **286**, 38–55 (2017)
69. K. Phan, A. Sgro, M.M. Maharaj, P. D'Urso, R.J. Mobbs, Application of a 3D custom printed patient specific spinal implant for C1/2 arthrodesis. J. Spine Surg. **2**(4), 314 (2016)
70. A. Dzian, J. Živčák, R. Penciak, R. Hudák, Implantation of a 3D-printed titanium sternum in a patient with a sternal tumor. World J. Surg. Oncol. **16**, 1–4 (2018)
71. S. Gerke, B. Babic, T. Evgeniou, I.G. Cohen, The need for a system view to regulate artificial intelligence/machine learning-based software as medical device. npj Digit. Med. **3**(1), 1–4 (2020). https://doi.org/10.1038/s41746-020-0262-2
72. S. Desai, M. Lovell, CFD analysis of a continuous inkjet print head for direct write fabrication, in *ASME International Mechanical Engineering Congress and Exposition*, vol. 43076, pp. 209–213 (2007)
73. J. Cordeiro, S. Desai, Process parameter studies of molecular dynamics models to control substrate wettability, in *International Manufacturing Science and Engineering Conference*, vol. 56826, p. V001T02A025 (2015)
74. J. Cordeiro, S. Desai, Exploring nano scale design space with molecular dynamics simulations, in *IIE Annual Conference Proceedings*, p. 856 (2015)
75. S. Desai, Methods and Apparatus for Manufacturing Micro-and/or Nano-Scale Features. Google Patents, 28 Nov 2013
76. S. Desai, M. Lovell, Modeling fluid–structure interaction in a direct write manufacturing process. J. Mater. Process. Technol. **212**(10), 2031–2040 (2012)
77. E. Adarkwa, S. Desai, Scalable droplet based manufacturing using in-flight laser evaporation. J. Nanoeng. Nanomanuf. **6**(2), 87–92 (2016)
78. S. Desai, M. Lovell, Multiphysics modeling of a piezoelectric bimorph disc in a direct write fabrication process, in *ASME International Mechanical Engineering Congress and Exposition*, vol. 42347, pp. 437–442 (2005)
79. S. Desai, M. Lovell, Coupled field analysis of a piezoelectric bimorph disc within a CIJ microfabrication process, in *IIE Annual Conference. Proceedings*, p. 1 (2006)
80. S. Murgu, H. Colt, Tracheobronchomalacia and excessive dynamic airway collapse. Clin. Chest Med. **34**(3), 527–555 (2013)
81. S. Desai, J. Perkins, B.S. Harrison, J. Sankar, Understanding release kinetics of biopolymer drug delivery microcapsules for

biomedical applications. Mater. Sci. Eng. B **168**(1–3), 127–131 (2010)
82. S.K. Parupelli, A. Aljohani, S. Desai, S. Khanal, N. Bhattarai, Direct jet printing and characterization of calcium alginate microcapsules for biomedical applications, in *IIE Annual Conference. Proceedings*, pp. 300–305 (2019)
83. S. Desai, A. Moore, B. Harrison, J. Sankar, Understanding microdroplet formations for biomedical applications, in *ASME International Mechanical Engineering Congress and Exposition*, vol. 48760, pp. 119–123 (2008)
84. S. Desai, J. Sankar, A. Moore, B. Harrison, Biomanufacturing of microcapsules for drug delivery and tissue engineering applications, in *IIE Annual Conference. Proceedings*, p. 507 (2008)
85. J.L. Perkins, S. Desai, B. Harrison, J. Sankar, Understanding release kinetics of calcium alginate microcapsules using drop on demand inkjet printing, in *ASME International Mechanical Engineering Congress and Exposition*, vol. 43871, pp. 77–82 (2009)
86. S. Bose, K.D. Traxel, A.A. Vu, A. Bandyopadhyay, Clinical significance of three-dimensional printed biomaterials and biomedical devices. MRS Bull. **44**(6), 494–504 (2019)
87. M. Zarek, N. Mansour, S. Shapira, D. Cohn, 4D printing of shape memory-based personalized endoluminal medical devices. Macromol. Rapid Commun. **38**(2), 1–6 (2017). https://doi.org/10.1002/marc.201600628
88. J. Li, C. Wu, P.K. Chu, M. Gelinsky, 3D printing of hydrogels: Rational design strategies and emerging biomedical applications. Mater. Sci. Eng. R Rep. **140**, 100543 (2020)
89. A. Kirillova, R. Maxson, G. Stoychev, C.T. Gomillion, L. Ionov, 4D biofabrication using shape-morphing hydrogels. Adv. Mater. **29**(46), 1703443 (2017)
90. H. Wei, Q. Zhang, Y. Yao, L. Liu, Y. Liu, J. Leng, Direct-write fabrication of 4D active shape-changing structures based on a shape memory polymer and its nanocomposite. ACS Appl. Mater. Interfaces **9**(1), 876–883 (2017)
91. M.S. Cabrera, B. Sanders, O.J.G.M. Goor, A. Driessen-Mol, C.W.J. Oomens, F.P.T. Baaijens, Computationally designed 3D printed self-expandable polymer stents with biodegradation capacity for minimally invasive heart valve implantation: a proof-of-concept study. 3D Print. Addit. Manuf. **4**(1), 19–29 (2017)
92. Y. Wang, H. Cui, T. Esworthy, D. Mei, Y. Wang, L.G. Zhang, Emerging 4D printing strategies for next-generation tissue regeneration and medical devices. Adv. Mater. **34**(20), 2109198 (2022)
93. U.S. Food and Drugs Administration, Laser Products and Instruments (2023), https://www.fda.gov/radiation-emitting-products/home-business-and-entertainment-products/laser-products-and-instruments.
94. US Food and Drugs Administration, Radiation-Emitting Electronic Products (2018), https://www.fda.gov/industry/regulated-products/radiation-emitting-electronic-products. Accessed 8 Jul 2022
95. U.S. Food and Drugs Administration, Device Classification Panels (2018), https://www.fda.gov/medical-devices/classify-your-medical-device/device-classification-panels.
96. U.S. Food and Drugs Administration, Product Code Classification Database (2018), https://www.fda.gov/medical-devices/classify-your-medical-device/product-code-classification-database.
97. US Food and Drug Administration, Premarket Notification 510(k), March 13 (2020), https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-notification-510k. Accessed 8 Jul 2022
98. US Food and Drug Administration, Postmarket Requirements (Devices) (2018), https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/postmarket-requirements-devices
99. U.S. Food and Drugs Administration, Reclassification (2021), https://www.fda.gov/about-fda/cdrh-transparency/reclassification
100. U.S. Food and Drugs Administration, Medical Device Accessories (2020), https://www.fda.gov/medical-devices/classify-your-medical-device/medical-device-accessories
101. U.S. Food and Drugs Administration, CFR—Code of Federal Regulations Title 21 (2023), https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=820.3
102. W. Gilmore, *The User-Computer Interface in Process Control: A Human Factors Engineering Handbook* (Elsevier, Amsterdam, 2012)
103. R. Gagnon et al., A user-centered evaluation of three intravenous infusion pumps, in *Proceedings of the Human Factors and Ergonomics Society Annual Meeting*, vol. 48, no. 15, pp. 1773–1777 (2004)
104. L. Lin, K.J. Vicente, D.J. Doyle, Patient safety, potential adverse drug events, and medical device design: a human factors engineering approach. J. Biomed. Inform. **34**(4), 274–284 (2001)
105. D. Sawyer, K.J. Aziz, C.L. Backinger, E.T. Beers, A. Lowery, S.M. Sykes, An introduction to human factors in medical devices, U.S. Department of Health and Human Services Public Health Service Food and Drug Administration Center for Devices and Radiological Health, p. 55 (1996)
106. N.E. Schaeffer, The role of human factors in the design and development of an insulin pump. J. Diabetes Sci. Technol. **6**(2), 260–264 (2012). https://doi.org/10.1177/193229681200600208
107. J.-E. Kim, L. Kessler, Z. McCauley, I. Niiyama, L.N. Boyle, Human factors considerations in designing a personalized mobile dialysis device: an interview study. Appl. Ergon. **85**, 103003 (2020)
108. R. North, C. Pospisil, R.J. Clukey, C.G. Parkin, Impact of human factors testing on medical device design: validation of an automated CGM sensor applicator. J. Diabetes Sci. Technol. **13**(5), 949–953 (2019). https://doi.org/10.1177/1932296819831071
109. A.L. Cassano, Applying human factors to the procurement of electrosurgical medical devices: a case study. Proceedings of the Human Factors and Ergonomics Society Annual Meeting **47**(15), 1815–1819 (2003)
110. C.J. Vincent, Y. Li, A. Blandford, Integration of human factors and ergonomics during medical device design and development: it's all about communication. Appl. Ergon. **45**(3), 413–419 (2014). https://doi.org/10.1016/j.apergo.2013.05.009
111. G. Ginsburg, Human factors engineering: a tool for medical device evaluation in hospital procurement decision-making. J. Biomed. Inform. **38**(3), 213–219 (2005). https://doi.org/10.1016/j.jbi.2004.11.008
112. J. Nielsen, R. Molich, Heuristic evaluation of user interfaces, in *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems*, pp. 249–256 (1990)
113. B. Schneiderman, *Designing the User Interface. Strategies for Effective Human–Computer Interaction* (Addison-Wesley, Hoboken, 1992)
114. M.-H. Maras, Internet of Things: security and privacy implications. Int. Data Priv. Law **5**(2), 99 (2015)
115. A. Chacko, T. Hayajneh, Security and privacy issues with IoT in healthcare. EAI Endorsed Trans. Pervasive Heal. Technol. **4**(14), 1–8 (2018). https://doi.org/10.4108/eai.13-7-2018.155079
116. F.Z. Amara, M. Hemam, M. Djezzar, M. Maimor, Semantic web and Internet of Things: challenges, applications and perspectives. J. ICT Stand. **10**(2), 261–292 (2022)
117. B. Pradhan, S. Bhattacharyya, K. Pal, IoT-based applications in healthcare devices. J. Healthc. Eng. **2021**, 6632599 (2021). https://doi.org/10.1155/2021/6632599
118. L.M. Dang, M.J. Piran, D. Han, K. Min, H. Moon, A survey on internet of things and cloud computing for healthcare. Electronics **8**(7), 768 (2019)

119. R. Hughes, *Patient Safety and Quality: An Evidence-Based Handbook for Nurses* (Agency for Healthcare Research and Quality, Rockville, 2008)
120. S.E. Bibri, Ethical implications of AMI and the IoT: risks to privacy, security, and trust, and prospective technological safeguards, in *The Shaping of Ambient Intelligence and the Internet of Things* (Atlantis Press, Paris, 2015), pp. 217–238
121. D.S. Punithavathani, K. Sujatha, J.M. Jain, Surveillance of anomaly and misuse in critical networks to counter insider threats using computational intelligence. Cluster Comput. **18**(1), 435–451 (2015)
122. B. Altubaishe, S. Desai, Multicriteria decision making in supply chain management using FMEA and hybrid AHP-PROMETHEE algorithms. Sensors **23**(8), 4041 (2023)
123. U.S. Food and Drugs Administration, Software as a medical device (SaMD) (2018), https://www.fda.gov/medical-devices/digital-health-center-excellence/software-medical-device-samd
124. US Food and Drugs Administration, Policy for device software functions and mobile medical applications. Guidance for Industry and Food and Drug Administration Staff (2019), https://www.fda.gov/media/80958/download
125. U.S. Food and Drugs Administration, Digital Health Criteria (2018), https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-criteria
126. International Medical Device Regulators Forum, Software as a medical device: possible framework for risk categorization and corresponding considerations (2014), http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-140918-samd-framework-risk-categorization-141013.pdf
127. US Food and Drugs Administration, What are examples of Software as a Medical Device? (2017) https://www.fda.gov/medical-devices/software-medical-device-samd/what-are-examples-software-medical-device
128. Y. Fang, D. Liu, Z. Jiang, H. Wang, Monitoring of sleep breathing states based on audio sensor utilizing Mel-Scale features in home healthcare. J. Healthc. Eng. **2023**, 6197564 (2023). https://doi.org/10.1155/2023/6197564
129. E.F. Camargos, F.M. Louzada, O.T. Nóbrega, Wrist actigraphy for measuring sleep in intervention studies with Alzheimer's disease patients: application, usefulness, and challenges. Sleep Med. Rev. **17**(6), 475–488 (2013)
130. S.-J. Zhou et al., Measuring sleep stages and screening for obstructive sleep apnea with a wearable multi-sensor system in comparison to polysomnography. Nat. Sci. Sleep **15**, 353–362 (2023). https://doi.org/10.2147/NSS.S406359
131. V. Patel, A. Chesmore, C.M. Legner, S. Pandey, Trends in workplace wearable technologies and connected-worker solutions for next-generation occupational safety, health, and productivity. Adv. Intell. Syst. **4**(1), 2100099 (2022)
132. Y. Xue, A review on intelligent wearables: Uses and risks. Hum. Behav. Emerg. Technol. **1**(4), 287–294 (2019)
133. M.C. Schall Jr., R.F. Sesek, L.A. Cavuoto, Barriers to the adoption of wearable sensors in the workplace: a survey of occupational safety and health professionals. Hum. Factors **60**(3), 351–362 (2018)
134. J. Kim et al., Simultaneous monitoring of sweat and interstitial fluid using a single wearable biosensor platform. Adv. Sci. **5**(10), 1800880 (2018)
135. A. Koh et al., A soft, wearable microfluidic device for the capture, storage, and colorimetric sensing of sweat. Sci. Transl. Med. **8**(366), 1-366ra165 (2016)
136. J. Kim et al., Non-invasive mouthguard biosensor for continuous salivary monitoring of metabolites. Analyst **139**(7), 1632–1636 (2014)
137. F. Güder et al., Paper-based electrical respiration sensor. Angew. Chem. Int. Ed. **55**(19), 5727–5732 (2016)
138. M. Padash, C. Enz, S. Carrara, Microfluidics by additive manufacturing for wearable biosensors: a review. Sensors **20**(15), 4236 (2020)
139. U.S. Food and Drugs Administration, Wireless Medical Device (2018), https://www.fda.gov/medical-devices/digital-health-center-excellence/wireless-medical-devices
140. P. Hamet, J. Tremblay, Artificial intelligence in medicine. Metabolism **69**, S36–S40 (2017). https://doi.org/10.1016/j.metabol.2017.01.011
141. L. Monostori, in Artificial Intelligence BT, in *CIRP Encyclopedia of Production Engineering*, ed. by L. Laperrière, G. Reinhart (Springer, Berlin, 2014), pp. 47–50
142. F. Jiang et al., Artificial intelligence in healthcare: past, present and future. Stroke Vasc. Neurol. **2**(4), 230–243 (2017)
143. A.M. Darcy, A.K. Louie, L.W. Roberts, Machine learning and the profession of medicine. JAMA **315**(6), 551–552 (2016)
144. H.J. Murff et al., Automated identification of postoperative complications within an electronic medical record using natural language processing. JAMA **306**(8), 848–855 (2011)
145. U.S. Food and Drugs Administration, Artificial Intelligence and Machine Learning in Software as a Medical Device (2021), https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device
146. Y. Xu et al., Artificial intelligence: a powerful paradigm for scientific research. Innovations **2**(4), 100179 (2021). https://doi.org/10.1016/j.xinn.2021.100179
147. M. Ogunsanya, S. Desai, Predictive modeling of additive manufacturing process using deep learning algorithm, in *IIE Annual Conference. Proceedings*, pp. 1–6 (2022)
148. H. Elhoone, T. Zhang, M. Anwar, S. Desai, Cyber-based design for additive manufacturing using artificial neural networks for Industry 4.0. Int. J. Prod. Res. **58**(9), 2841–2861 (2020)
149. T. Akter, S. Desai, Developing a predictive model for nanoimprint lithography using artificial neural networks. Mater. Des. **160**, 836–848 (2018)
150. S. Desai, C. Dean, Y. Desai, Cyber-enabled concurrent material and process selection in a flexible design for manufacture paradigm. Int. J. Adv. Manuf. Technol. **97**(5–8), 1719–1731 (2018)
151. K.W. Johnson et al., Artificial intelligence in cardiology. J. Am. Coll. Cardiol. **71**(23), 2668–2679 (2018). https://doi.org/10.1016/j.jacc.2018.03.521
152. A.-M. Singeap, C. Stanciu, A. Trifan, Capsule endoscopy: the road ahead. World J. Gastroenterol. **22**(1), 369 (2016)
153. B. Sushma, P. Aparna, Recent developments in wireless capsule endoscopy imaging: Compression and summarization techniques. Comput. Biol. Med. **149**, 106087 (2022). https://doi.org/10.1016/j.compbiomed.2022.106087
154. D. Nikolayev, M. Zhadobov, R. Sauleau, P. Karban, Antennas for ingestible capsule telemetry, in *Advances in Body-Centric Wireless Communication: Applications and State-of-the-Art* (IET, London, 2016), pp. 143–186
155. P.P. Stanich, B. Kleinman, K. Betkerur, N. Mehta Oza, K. Porter, M.M. Meyer, Video capsule endoscopy is successful and effective in outpatients with implantable cardiac devices. Dig. Endosc. **26**(6), 726–730 (2014)
156. I. Tziortziotis, F.-M. Laskaratos, S. Coda, Role of artificial intelligence in video capsule endoscopy. Diagnostics **11**(7), 1192 (2021)
157. G.S. Raju, L. Gerson, A. Das, B. Lewis, American Gastroenterological Association (AGA) Institute technical review on obscure gastrointestinal bleeding. Gastroenterology **133**(5), 1697–1717 (2007)
158. H. Bay, A. Ess, T. Tuytelaars, L. Van Gool, Speeded-Up Robust Features (SURF). Comput. Vis. Image Underst. **110**(3), 346–359 (2008). https://doi.org/10.1016/j.cviu.2007.09.014

159. D.K. Iakovidis, S. Tsevas, A. Polydorou, Reduction of capsule endoscopy reading times by unsupervised image mining. Comput. Med. Imaging Graph. **34**(6), 471–478 (2010). https://doi.org/10.1016/j.compmedimag.2009.11.005
160. H.-G. Lee, M.-K. Choi, B.-S. Shin, S.-C. Lee, Reducing redundancy in wireless capsule endoscopy videos. Comput. Biol. Med. **43**(6), 670–682 (2013). https://doi.org/10.1016/j.compbiomed.2013.02.009
161. S.C. Payne, J.B. Furness, M.J. Stebbing, Bioelectric neuromodulation for gastrointestinal disorders: effectiveness and mechanisms. Nat. Rev. Gastroenterol. Hepatol. **16**(2), 89–105 (2019)
162. D. Miley, L.B. Machado, C. Condo, A.E. Jergens, K.-J. Yoon, S. Pandey, Video capsule endoscopy and ingestible electronics: emerging trends in sensors, circuits, materials, telemetry, optics, and rapid reading software. Adv. Devices Instrum. (2021). https://doi.org/10.34133/2021/9854040
163. T. Nakamura, Capsule endoscopy in Japan. Dig. Endosc. **34**, 76–78 (2022)
164. J. Park et al., Recent development of computer vision technology to improve capsule endoscopy. Clin. Endosc. **52**(4), 328–333 (2019)
165. X. Jia, M.Q.-H. Meng, Gastrointestinal bleeding detection in wireless capsule endoscopy images using handcrafted and CNN features, in *2017 39th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pp. 3154–3157 (2017). https://doi.org/10.1109/EMBC.2017.8037526
166. Y. Yuan, M.Q. Meng, Deep learning for polyp recognition in wireless capsule endoscopy images. Med. Phys. **44**(4), 1379–1389 (2017)
167. D.K. Iakovidis, A. Koulaouzidis, Software for enhanced video capsule endoscopy: challenges for essential progress. Nat. Rev. Gastroenterol. Hepatol. **12**(3), 172–186 (2015). https://doi.org/10.1038/nrgastro.2015.13
168. Z. Ding et al., Gastroenterologist-level identification of small-bowel diseases and normal variants by capsule endoscopy using a deep-learning model. Gastroenterology **157**(4), 1044–1054 (2019)
169. T. Aoki et al., Clinical usefulness of a deep learning-based system as the first screening on small-bowel capsule endoscopy reading. Dig. Endosc. **32**(4), 585–591 (2020)
170. G. Ciuti et al., Frontiers of robotic endoscopic capsules: a review. J. Micro-bio Robot. **11**, 1–18 (2016)
171. J.C. Norton et al., Intelligent magnetic manipulation for gastrointestinal ultrasound. Sci. Robot. **4**(31), eaav7725 (2019)
172. J. Min, Y. Yang, Z. Wu, W. Gao, Robotics in the gut. Adv. Ther. **3**(4), 1900125 (2020)
173. U.S. Food and Drugs Administration, Ingestible telemetric gastrointestinal capsule imaging system—final class ii special controls guidance document for industry and FDA (2018), https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/ingestible-telemetric-gastrointestinal-capsule-imaging-system-final-class-ii-special-controls
174. B. Prabhakar, R.K. Singh, K.S. Yadav, Artificial intelligence (AI) impacting diagnosis of glaucoma and understanding the regulatory aspects of AI-based software as medical device. Comput. Med. Imaging Graph. **87**, 101818 (2021). https://doi.org/10.1016/j.compmedimag.2020.101818
175. X. Zhang et al., Prevalence of diabetic retinopathy in the United States, 2005–2008. JAMA **304**(6), 649–656 (2010)
176. Cruise Ophthalmic, Portable eye fundus camera Digital Retinal Scan Photography. https://www.aliexpress.com/item/3256801216401596.html?gatewayAdapt=4itemAdapt
177. Digital Diagnosis-AI the right way. https://www.digitaldiagnostics.com/products/eye-disease/idx-dr/?gclid=CjwKCAjw46CVBhB1EiwAgy6M4hNGGgKBv1kg0j_9nkFxQHp5UqBclhg-5WyP8KGTFVOLrpYWTGp7fRoCuPIQAvD_BwE
178. F. Mahgoub, Here's How the FDA Approval of IDx-DR Will Impact Patients (2018), https://introwellness.com/eyes/idx-dr/
179. E.H. Nepal, Review of 3nethra Classic Digital Non-mydriatic Fundus Camera (2021), https://www.eyehealthnepal.com/3nethra-classic-fundus-camera/
180. L. Tsang et al., The impact of artificial intelligence on medical innovation in the European Union and United States. Intellect. Prop. Technol. Law J. **29**(8), 3–12 (2017)
181. U.S. Food and Drugs Administration, Device Software Functions Including Mobile Medical Applications (2022), https://www.fda.gov/medical-devices/digital-health-center-excellence/device-software-functions-including-mobile-medical-applications
182. U.S. Food and Drugs Administration, Medical Device Data Systems (2019), https://www.fda.gov/medical-devices/general-hospital-devices-and-supplies/medical-device-data-systems
183. G. Freckmann et al., Insulin pump therapy for patients with type 2 diabetes mellitus: evidence, current barriers, and new technologies. J. Diabetes Sci. Technol. **15**(4), 901–915 (2021)
184. N.J. Wimmer et al., Assessing the cost burden of United States FDA-mandated post-approval studies for medical devices. J. Health Care Finance **2016**(Spec FEATURES) (2016)