From Wearable Sensors to Smart Implants – Towards Pervasive and Personalised Healthcare

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Abstract—Objective: **This article discusses the evolution of pervasive healthcare from its inception for activity recognition using wearable sensors to the future of sensing implant deployment and data processing.** ***Methods:*** **We provide an overview of some of the past milestones and recent developments, categorised into different generations of pervasive sensing applications for health monitoring. This is followed by a review on recent technological advances that have allowed unobtrusive continuous sensing combined with diverse technologies to reshape the clinical workflow for both acute and chronic disease management. We discuss the opportunities of pervasive health monitoring through data linkages with other health informatics systems including the mining of health records, clinical trial databases, multi-omics data integration and social media.** ***Conclusion:*** **Technical advances have supported the evolution of the pervasive health paradigm towards preventative, predictive, personalised and participatory medicine.** ***Significance:*** **The sensing technologies discussed in this paper and their future evolution will play a key role in realising the goal of sustainable healthcare systems.**

***Index Terms*— pervasive health, wearable sensors, implantable sensors, health informatics.**

I. Introduction

ESCALATED incidence and costs associated with chronic symptoms, senescence-related dependence, lifestyle induced poor health (*e.g.* obesity), and non-communicable diseases such as cancer and cardiovascular diseases are major healthcare challenges globally. Rather than relying on delayed intervention and expensive treatments, the future of a sustainable global healthcare system is one that is specifically focused on *prevention, early detection and minimally invasive* management of diseases. Recent advances in sensing technologies have made it possible to monitor health in an unobtrusive and seamless manner, transforming episodic, largely manual sampling processes to continuous, context-aware monitoring and intelligent intervention. Figure 1 outlines the evolution of allied technologies in the last 10 years. Three factors in particular have contributed to these advances: 1) increased data processing power, 2) faster wireless communications with higher bandwidth, and 3) improved design of microelectronics and sensor devices. The first two represent general trends in computing, whereas the third is of particular interest to pervasive health. Advances in sensor electronics have supported the development of a wide range of embedded systems, as well as devices that are small, lightweight and can be comfortably worn by an individual or ubiquitously placed in the environment with minimal power consumption.

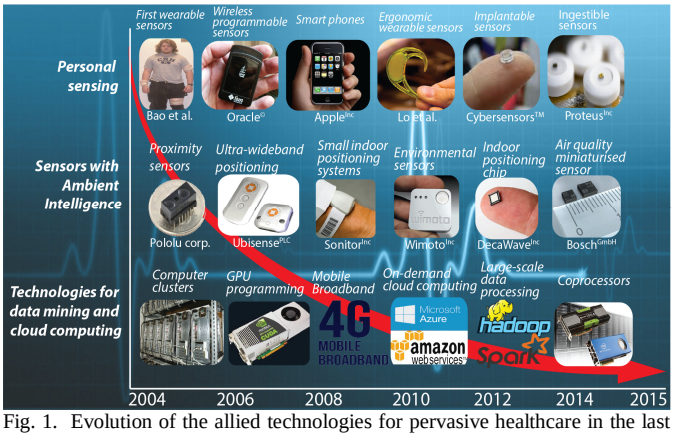

Fig. 1. Evolution of the allied technologies for pervasive healthcare in the last from 2004 to 2015.

Thus far, *wearable devices* are widely used to measure key health indicators such as electrocardiogram (ECG), heart rate, blood pressure, blood oxygen saturation (SpO2), body temperature, postures and physical activities (see Table I). Likewise, ambient sensing systems are now embedded in homes and affixed to doors, beds [1], mattresses [2], toilets [3], wardrobes [4] and electrical appliances [5]. The wearable systems supported by ambient sensing have the capability to *continuously* monitor human physiology and dysfunction enabling critical events such as myocardial infarction, arrhythmias and strokes to be captured and consequently expediting treatments and saving lives [6]. Health and wellbeing can be similarly monitored and seamlessly tracked, motivating high-risk groups such as people with higher than normal body mass indices to engage in physical activity and adopt a change in lifestyle. These relatively simple interventions may improve cardiovascular and bone health, reduce dependence, escalated healthcare costs and morbidity of lifestyle-induced poor health.

Advances in technologies are largely underpinned by recent improvements in low-power micro-electronics, fabrication, and packaging for device miniaturisation. In addition to developments in micro-fabrication and nanofabrication, new designs in biocompatible materials and sensors for minimising foreign body reactions to implants, adaptive management of sensor drift and accelerated data transmission from inside the body, have propelled recent advances in implantable biosensors. Clinically, implantable *sensors* can better address the challenges of chronic disease monitoring, capture critical events, enhance personalisation of surgically implanted

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prosthetics and critically accelerate the detection of failing implants thereby minimising healthcare hazards. Patients with diabetes would no longer have to undergo painful blood capillary tests or inject insulin if an intelligent implantable device could sense blood glucose levels and respond accordingly. White blood cells and neutrophil counts could be continually monitored in patients undergoing chemotherapy cycles such that the earliest sign of neutropenia could be coupled with granulocyte stimulation to prevent sepsis. Implantable sensors that monitor the axial load on an individual subject's spine may lead to personalised orthopaedic prostheses. Similarly, analgesic drug delivery may be tailored to the individual based on data from implanted sensors in the central and peripheral nervous systems. Rapid automated detection of failing prosthetics may prevent health risks such as that exemplified by Poly Implant Prothèse (PIP) implants in which breast prostheses with a significantly higher risk of rupture were implanted into thousands of women worldwide. Fabricating sensors within implants may have accelerated detection of rupture and may have provided rapid reassurance to those women with intact prostheses. Regardless of the healthcare application, or whether the sensors are wearable, implantable or placed in the ambient surroundings, three different generations of development can be considered as shown in Figure 2. In the following sections, we discuss the evolution of the pervasive health paradigm as well as the technical implications, with a particular focus on the future of pervasive health monitoring.

II. Evolution of Pervasive Health Applications

A. First Generation

In *first generation* applications, the architectural system typically consists of a *single sensing modality* with wireless connectivity being able to make predictions about activities or health status. Notable first generation devices applications include daily activity recognition from wearable motion sensors or sensors embedded in the environment [7]; gait analysis from wearable sensors [8] or those embedded in the flooring of a smart house [9]. Whilst the amount of data processed from wearable sensors that can be stored is limited to several megabytes, applications based on video and/or audio signals can generate up to hundred megabytes of data [10]. Processing is typically performed centrally, relying on off-line, retrospective batch processing.

B. Second Generation

The *second generation* of wireless monitoring devices emerged as a result of advances in sensing technology that facilitate *continuous monitoring* with multiple sensors, each of them being responsible for providing inference, either from wearable or ambient sensors. With this generation, we introduce the concept of *agents*, which are processing entities that, in addition to sensing, may take the necessary actions towards an objective. These actions can be based on an autonomous interaction with the environment or cooperation with other agents. Integrating the outputs from a diverse range of intelligent agents therefore requires a higher level of reasoning than in first generation devices. The objective is to reduce the uncertainty of predictions by fusing multimodal information and/or providing a sense of *context-awareness*, which can improve the level of integration of the application with the monitored scenario. For instance, a sleep disorder monitoring was developed in [11] using a combination of wearable, light sensors and video recordings in order to detect the most relevant events during sleep and allow long-term monitoring. In another example, a fall detection system using information from wearable motion and ambient vision sensor as well as energy consumption (appliances and lights turned on and off) was able to appreciate the context of a fall in order to recognise environmental hazards [12]. Typically, the data acquired from such applications may be up to several hundreds of megabytes or even several gigabytes [13].

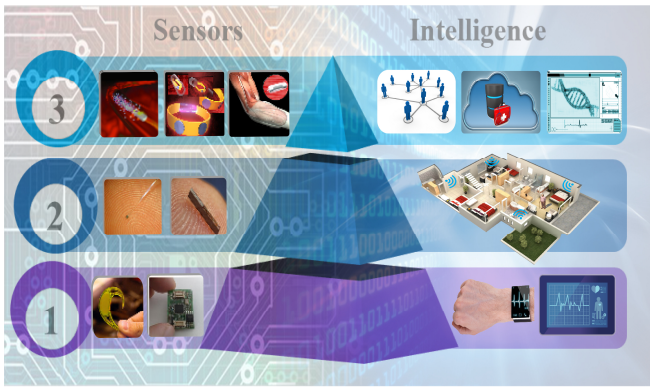

Fig. 2. A schematic overview of the three generations of advances in *sensor technology* (left side) and *data analytics and intelligent systems* (right side). On the left, the figure displays small low-powered sensors (1st layer), ultra-low powered micro-sensors (2nd layer), and biologically-powered micro-implants and nano-scale devices (3rd layer). On the right, the figure represents single sensor monitoring systems (1st layer), continuous monitoring with multiple sensors in an environment enabling context-awareness (2nd layer) and pervasive health combined with other big data health sources enabling integrated care (3rd layer).

C. Third Generation

The *third generation* is a nascent research area that aims to combine continuous health monitoring with other sources of medical knowledge. In addition to the aforementioned pervasive sensing modalities of the first and second generations, the objective in third-generation applications is to integrate intelligent agents that implement technologies such as stream processing, data mining, genetic and multi-omics data. These agents are thus responsible for extracting information from a variety of sources including clinical research, patient records, laboratory generated data (*e.g.* genomics, proteomics, metabonomics). Through effective fusion of multi-modal information, the system examines patients from a system level with all compounding factors taken into account [34]. This will support the decision-making process governed by the latest evidence in biomedical and health informatics. Integrating knowledge from multiple sources has great potential to improve and personalise clinical care.

TABLE I
EXEMPLAR WEARABLE AND IMPLANTABLE SENSORS DEVELOPED IN RECENT YEARS AND THEIR CLINICAL APPLICATIONS

Sensor placement		Sensors type	Key technical features	TRL	Clinical focus
Chest, torso		▪ ECG/PPG (CardioMem®,[14, 15]) ▪ Glucose (Dexcom®) ▪ Adenosine triphosphate [16] ▪ Accelerometer [17] ▪ Galvanic skin response (GSR) [15] ▪ Temperature [18]	▪ Electrodes on conductive fabric/flexible "heart sock". ▪ Glucose needle patch. ▪ Tested on mouse model with air pouch. ▪ Flexible system with middleware. ▪ "Smart Vest" with multi-parameter monitoring. ▪ Temperature patch.	▪ 9 (CardioMem®), 6 [14, 15] ▪ *9* ▪ 9 ▪ 6 ▪ 6 ▪ 6	▪ Cardiac arrhythmia [14, 15] ▪ Diabetes. (Dexcom®) ▪ Inflammation [16] ▪ Rehabilitation [17] ▪ Obesity [15] ▪ Infection [18]
Head	*Eye*	▪ Intraocular pressure (IOP) [19] ▪ Glucose (Google® contact lens)	▪ IOP by change in corneal curvature. ▪ RFID readout.	▪ *6* ▪ *5*	▪ Glaucoma [19] ▪ Diabetes (Google®)
	Brain	▪ Impact force (Checklight™) ▪ Glucose/lactate (Pinnacle™) ▪ EEG (NeuroPro™)	▪ Impact logging. ▪ Rat head capsule with multichannel potentiostat. ▪ 8 channel EEG.	▪ *9* ▪ *9* ▪ *7*	▪ Concussion (Checklight™) ▪ Trauma/haemorrhage (Pinnacle™) ▪ Epilepsy (NeuroPro™)
	Ear	▪ Acceleration [8, 20] ▪ Audio [21]	▪ Three axis accelerometer behind the ear. ▪ Binaural hearing aid.	▪ *8* ▪ *6*	▪ Clinical gait analysis [8, 20] ▪ Hearing loss [21]
	Tooth	▪ Bacteria [22]	▪ Anti-microbial peptide coated grapheme as bacterial sensor. Read out with battery-less wireless interrogation.	▪ *6*	▪ Infection [22]
Musculoskeletal	*Wrist/arm*	▪ Activity levels/energy expenditure (Nike®) ▪ Skin conductance [23] ▪ Accelerometer [24, 25] ▪ Gyroscope and magnetometer[26] ▪ EMG and EEG [25]	▪ Custom metric for energy expenditure. ▪ Soft wrist band for electrodermal activity. ▪ Accelerometer network on limbs. ▪ Wrist/elbow mounted motion tracker. ▪ Multi-modal flexible/conformal patch.	▪ 9 ▪ 6 ▪ 6 ▪ 6 ▪ 6	▪ Obesity (Nike®) ▪ Emotional stress [23] ▪ Parkinson's disease [24, 25] ▪ Stroke rehabilitation [26] ▪ Neo-natal ICU [25]
	Feet	▪ Accelerometer [24, 27] ▪ Gyroscopes force, bend and pressure, electric field height, air pressure [28]	▪ Posture/activity from heel acceleration and planar pressure. ▪ Gait shoe monitors in-shoe air pressure for ground contact force.	▪ *6* ▪ *6*	▪ Obesity [24, 27] ▪ Clinical gait analysis [28]
	Hand/fingers	▪ Blood pressure, SpO_2 (iHealth®) ▪ Accelerometer [29, 30] ▪ Bend/force [30]	▪ Wireless finger cap and pressure cuff. ▪ Sensor network on glove for hand gesture analysis. ▪ Pressure sensor network glove measuring range of motion.	▪ *9* ▪ 6 ▪ *6*	▪ Hypertension (iHealth®) ▪ Surgical training [29, 30] ▪ Arthritis [30]
Hip		▪ Vibration [31]	▪ Hip prosthesis tested with artificial thigh.	▪ *6*	▪ Hip prosthesis [31]
Implantable/Ingestible wireless sensors/stimulators		▪ pH [32] ▪ Temperature, HR/respiration (VitalSense®) ▪ Heart rhythm (Evera™) ▪ Auditory nerve (Cochlear®) ▪ Visible light (SecondSight®) ▪ Brain stimulator (Soletra®) ▪ Medicine ingestion (Proteus®) ▪ Force sensor [33] ▪ Pressure sensor (Carmat™)	▪ pH capsule attached to oesophageal wall. ▪ Ingestible capsule for wireless core temperature. ▪ Implantable defibrillator. ▪ Auditory nerve stimulation with wireless powering. ▪ Retinal ganglion cells (RGC) stimulation. ▪ Single lead implantable neurostimulator. ▪ Ingestible pill with wireless interrogation for ingestion signatures. ▪ Battery-less piezoelectric energy harvester knee implant. ▪ Complete artificial heart.	▪ *9* ▪ *9* ▪ *9* ▪ *9* ▪ *9* ▪ *9* ▪ *8* ▪ *6* ▪ *6*	▪ GERD [32] ▪ Infection (VitalSense®) ▪ Cardiac arrhythmia (Evera™) ▪ Deafness (Cochlear®) ▪ Blindness (SecondSight®) ▪ PD, Tremor (Soletra®) ▪ Tablet ingestion management (Proteus®) ▪ Knee replacement surgery [33] ▪ Heart replacement (Carmat™)
Wearable for ambient environment		▪ Ozone Chlorine, Methane, Carbon monoxide, humidity, temperature (Sensordrone®)	▪ Environmental sensing link with smartphones.	▪ *9*	▪ Poisoning (Sensordrone®)

For example, family history data combined with personal genome analysis has the potential to integrate disease risks across multiple known polymorphisms [35]. In particular, variants of known pharmacogenetic importance may lower or raise the threshold for treatments [36]. Patients at seemingly low risk of cardiovascular disease can be identified for treatment once family history, global genetic risk and genomic predictors of response to therapy are considered. Identifying patients with a disease variants known for drug resistance may lead to decisions to alter pharmacological interventions or increase the dose of medication (e.g. CYP2C19 and clopidogrel [35]).

III. Advances in Sensing and Hardware Design

Due to consumer demand and a shift in research landscape, the evolution of sensing hardware in the past decade has been accelerated. In Table I, we summarise some of the state-of-the-art developments in sensing hardware covering devices used in research as well as products available from the industry. The table is organised into categories according to sensor placements, from torso mounted wearable sensors to sensors placed on a finger. The clinical relevance of each reported sensing hardware is included at the end of each row. This ranges from activity recognition to tackle obesity to potential infection detection by measuring core body temperatures. In addition to wearable sensors, implantable and ingestible wireless sensing hardware examples are equally included. The main application of these implantable sensors is to act as loss-of-function replacement prosthesis or for chronic disease management. For each category, the example devices are arranged in decreasing Technological Readiness Levels (TRL) with TRL=4 indicating in-lab component validation through to TRL=9 where technology is in its final form, being used under operational conditions. Platform technologies that underpin the advance of sensing hardware can be categorised as developments in sensor embodiment technology, micro-electronics and fabrication processes, and the availability of wireless power delivery towards miniaturised implantable sensors. In the following sections, we summarise these technological advancements that give rise to current state-of-the-art sensing systems and beyond.

A. Sensors and Sensor Embodiment

Traditionally, wireless sensing nodes comprised of sensors, processing and wireless electronics assembled on printed circuit boards (PCBs) made of glass-refined epoxy laminate (FR4). Recently, flexible materials such as polyimide [37, 38] have been used for sensor node platforms. These flexible sensor node assemblies facilitate flexible sensor embodiment and ultimately allow easier sensor application on the human body in the form of a conformal “patch”. On the other hand, a recent trend in low-cost sensor patch embodiments is to realise microfluidic channels, printed sensors and electronics on the same engineered paper substrate [39]. Thus liquid flow systems are constructed on paper by taking advantage of hydrophilic channels. In this case, liquid is driven by capillary forces, therefore eliminating the need for pumps used in traditional bulk-based microfluidic devices. Biochemical sensing of ions, glucose, and lactate have been demonstrated on a paper microfluidic device for point-of-care diagnostic applications [40]. For the low-cost integration of electronic components, various nanoparticles have been printed to construct conductive tracks and passive electronic components as well as strain/temperature sensors [41]. A related trend to paper based microfluidic sensors concerns smart textiles, where force, chemical, humidity and temperature sensors have been realised in wearable fabrics. Two approaches exist in functionalising fabric for sensing purposes; one being the attachment of discrete sensors to existing fabrics while the other one involves applying coatings to the fabric via means such as screen/ink-jet printing and electrodeposition. Sensor read-out circuits can also be integrated into fabrics through weaving or knitting conductive threads with conventional fabric materials [42]. Recent advances in material science have also enabled the realisation of *epidermal electronics and sensors* [43] for monitoring tissues and organs in an implantable device setting. These are thin film sensor devices fabricated on substrates with only ~20µm thickness. A range of sensors including pH, temperature, strain, ECG, and PPG are integrated with microstructures to provide electrical, thermal and optical stimulation. These sensors and stimulators are all assembled on the same flexible-conformal substrate for cardiac monitoring [14].

Soft lithography is the key enabling technology behind epidermal sensors [44]. These were developed specifically for micro/nano-processing of flexible thin film materials such as polymers as opposed to traditional lithography techniques mainly used for processing bulk silicon for integrated circuits. Notable soft lithography techniques include moulding, embossing, and transfer-printing with polymeric stamps. These techniques have been used to successfully integrate sensor electrodes with microfluidic devices in the micro-nano scale [45]. Soft lithography processing has been used in conjunction with traditional lithography processing such as photolithography and physical vapour metal deposition to realise bioresorbable devices [46]. These bioresorbable sensing platforms are engineered by depositing organic semiconductor materials or thin film semiconductor materials on biodegradable substrates to form complete systems of sensors and electronic components. These systems are thus dissolvable in salt solutions given exposure times from a few hours to weeks. As well as wireless-wearable sensing, bioresorbable sensors and electronics have tremendous potential in the area of transient implants where only short-term implantation is required to monitor post-operative infection. Another area of active research in advanced materials for sensors is self-healing structures [47]. These are largely based on self-adhesion on flexible substrates by conductive particle embedded organic polymers. These polymers consist of reversible hydrogen-bonding networks that can dynamically associate/dissociate with external disturbances, providing the self-healing capabilities. These self-healing materials will facilitate the development of next generation, fully integrated, robust sensing platforms with minimum sensor drift and ambiguity, as well as self-powered electronic readouts.

B. *Micro-electronics and Fabrication*

Advances in *Application Specific Integrated Circuit* (ASIC) technology [48] have paved the way for wireless sensing platform development towards minimum size, minimum power consumption as well as minimising measurement uncertainty. A typical System-on-Chip (SoC) ASIC consists of sensor signal conditioning circuits, microcontroller, and radio communication circuitry supporting devices applications throughout generations I-III. The available silicon resource facilitates the deployment of low-power, mixed-mode, analogue/digital *on-node processing* to maximise the mutual information between the input signals and the output variables and support data reduction at source. With the advent and increased availability of microfabrication techniques, the sensor ASIC can also be used as a substrate for fabricating additional sensors. This leaves the overall sensor and processing/radio circuitry footprint being not much larger than the typical ASIC die, which is in the region of less than 1cm^2. Specifically, special fabrication processes integrate physical microelectromechanical (MEMs) sensors [49] such as strain gauge, pressure sensors and inertia sensors on the same ASIC silicon substrate [50]. It is also not uncommon to carry out post-processing to deposit biochemical sensing elements on top of ASICs [51]. Example applications of biochemical sensor integration include "on-chip" sensors for DNA detection, as well as neurotransmitter and proteomic measurements through on-chip sensing microstructures such as nanowires and carbon nanotubes [52-54]. The signal transduction process for DNA detection involves immobilised oligonucleotides on a metal surface (e.g. gold). The specific binding of the target oligonucleotide to the probe creates a change in charge or capacitance at the electrode surface. This change in charge or capacitance is then sensed by the read-out circuitry. In many cases, the metal probe residing the immobilised oligonucleotides consists of modified metal tracks on a micro fabricated integrated circuit. This setup with close proximity between the sensors and interfacing ASIC also improves sensor signal integrity. In the case where the sensors and ASIC can only be fabricated using their respective optimum technologies, advanced integration processes known as *System-in-Package* (SiP) [55, 56] are used to drastically reduce sensing system footprint compared to traditional horizontal assembly with PCBs. To this end, SiPs employ vertical stacking of silicon bare-dies or packaged sensors/chips.

C. *From Wearables to Implantables*

Recent interests in published materials and patents on technologies related to wearable-implantable sensors are shown in Figure 3. Smart sensing and stimulation implant technologies are essential for managing a large number of critical chronic diseases. They also play an increasingly important role in post-surgical infection prevention. As an example, in the UK alone tens of thousands of pacemakers are implanted each year [57]. On the other hand, despite increasing sophistication of surgical interventions, surgical site infection occurs in 2-5% of all surgical hospitalisations, accounts for 17% of all hospital acquired infections and burdens approximately 20% of high-risk surgical patients [58]. The deployment of wearable/implanted sensors serves to help understand, model, predict and ultimately minimise post-operative complications and avoid patient readmission. The challenge of chronic sensing implants remains to be in the areas of long-term sensor stability, power management of active implants, and biocompatibility of embodiment. To this end, active sensor management schemes can be used to mitigate sensor degradation due to biofouling [59]. For active implants requiring an energy source, wireless power transmission ultrasultra [60] or ultrasonic [61] links doubling as a data-communication path can be deployed as a wireless battery charger for critical/non-interruptible implants such as a pacemaker. Biocompatible materials such as Parylene and Liquid Crystal Polymer (LCP) [62] can be used to encapsulate the sensor implant. Implants capable of sensing post-surgical infection and monitoring tissue healing should be transient in nature and must be extracted without the need for re-operative intervention. To this end, biodegradable [46] technologies serve as a promising platform for further investigation.

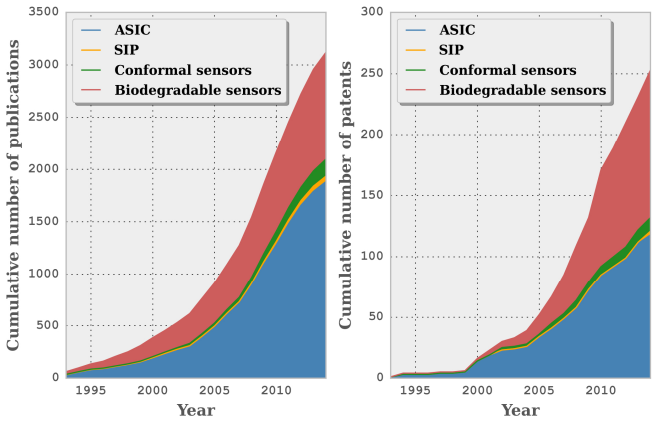

Fig. 3. Evolution of academic publication trends (left) and issued patent trends (right) in sensor hardware in the last 20 years, showing the rapid development in ASIC design and biodegradable sensor in both academic and commercial sectors. Publication data were collected from the following databases: IEEE Explorer, ACM Digital library, PubMed (National Library of Medicine, Bethesda, MD), Web of Science and Scopus. Patent data were collected from the European Patent Office master documentation database (called DOCDB).

D. *Data Management and Sensor Informatics*

The evolution of the sensing devices towards pervasive data capture and heterogeneous data integration has introduced significant challenges in data management and analytics for decision support. Early systems involved relatively small-scale data, often processed via off-line, retrospective analysis. The ability of real-time data capture and the need for integration with a diverse range of heterogeneous data sources has presented unique challenges in sensor informatics [63].

The management of preeclampsia (a pregnancy-related disorder which if allowed to progress to eclampsia potentially risks the life of the mother and foetus), for example, may be optimised by incorporating mobile home-monitoring data, physiological knowledge and disease factors such as risks and treatment side effects [64]. For Intensive Care Units (ICU), it is possible to fuse information from all bedside sensors, lab results and electronic patient records [65].

Increasingly, we are dealing with big databases and clinical decision support is no longer limited to isolated data sources and data abstraction can start right from the node level,

allowing on-node processing combined with the latest advances in mixed signal ASIC with algorithms mapped directly to the silicon level to achieve ultra-low-power high-throughput processing.

E. Sources of Data and Heterogeneity

The integration of multiple information databases to combine with information from pervasive health sensors provides several opportunities as well as important challenges. Effective integration of the myriad of sensing data with existing biomedical databases requires specific considerations. *Electronic health records* (EHRs) describing treatments and patient outcomes are rich but under-utilised. Mining local information included in EHR data-aware houses has already proved an effective way of managing a wide range of healthcare challenges such as supporting disease management system [66, 67], pharmacovigilance [68], building models for predicting health risk assessment [69, 70], communicating survival rates [71, 72], making therapeutic recommendations [71, 73], discovering co-morbidities and building support systems for clinical trial recruitment [74]. When longitudinal health data are sampled in a continuous fashion, meaningful and rich time-series can be collected in order to enable temporal data mining. This feature can be useful to identify patterns in patient trajectories through treatments, diseases and intervention timelines.

Clinical research databases can be used to provide rapid answers to queries such as possible drug interactions, risk factors, indicator thresholds and disease signatures. A good example of a clinical research database is ClinicatTrials.gov [75]. Trials are usually performed in multiple study sites and analysis might be provided by diverse labs. This issue brings more complexity to an already heterogeneous dataset. Multiple participants can be recruited simultaneously and equipped with a pervasive health monitoring system that can be set-up to automatically collect the desired data in distributed but synchronized schedules, removing the effect of different environmental conditions and seasons. This streamlines and accelerates data collection protocols. Data mining over trial data has been proposed as a method to identify predictive biomarkers of a treatment effect [76] or determining relevant groups of interest [77] by combining the details from several studies. These indicators may serve to specify the set of biomedical markers of interest where a pervasive health monitoring system can subsequently place special emphasis on.

Multi-omics acquisition and profiling will enable the full potential of EHR to be realised. Combining the effect of these new features with pervasive health monitoring may enable rapid gathering of necessary information to understand sequence variances in the human genome. Although genotyping is still a relatively new field in EHR, it has great potential for genetic stratification in patient screening, for instance in the case of factors arising from genotyping such as high-risk DNA mutations, milk and gluten intolerance and mucoviscidosis. In current practice, screening for genetic anomalies takes several weeks, and often requires a priori information regarding the mutation to be screened. The delays incurred not uncommonly restrict treatment options and impact on decision-making. The cost and time required for genotyping and genome sequencing have both reduced. Indeed, in recent years there has been major interest in lab-on-a-chip approaches for DNA sensing [78]. This sensing modality aims at detecting disease-related nucleotide variations which could, for example, contribute to disease susceptibility or reaction to pathogens and drugs. Consider a patient diagnosed in her forties with unilateral breast cancer (receptor triple negative) who also has a strong family history of breast and ovarian cancer, prompting her surgeon to consider whether or not to prophylactically treat her 'healthy' contralateral breast. Currently, she would qualify for gene testing but the results may take over a month leading to inevitable treatment delays. Faced with this dilemma she may decide to have unilateral surgery and delay testing. Subsequently she is found to have a high-risk breast cancer mutation (e.g. BRCA1) and undergoes a delayed contralateral mastectomy. In the future, on-chip sequencing would enable rapid detection of risk mutations simultaneous with a cancer diagnosis and the patient can better decide whether to undergo simultaneous bilateral mastectomy and reconstruction. Such a patient if found to have a risk mutation may want to rapidly access the location of support groups and other sufferers in an extended network.

One important yet emerging source of information for pervasive health is the one provided by *social network data*. In healthcare, social network data have helped understand the evolution of diseases and unhealthy habits from geographical, behavioural and time viewpoints. For example, collective dynamics from people suffering from obesity and smokers, have been assessed using social network [79]. It has also been used in health crises and epidemic studies such as in the case of severe acute respiratory syndrome, H1N1 influenza, tuberculosis outbreaks [80, 81], and more recently muted to track Ebola [82]. The rapid availability of social network data can be effectively combined with pervasive health monitoring, for example assessing the current health status of a patient with their interactions with other individuals and the effects that these ones induce in their health status.

F. Data Processing and Analysis

Figure 4 shows the research trends in the data analysis frameworks used for clinical decision support systems with an exponential increase in interest in this area and a greater variety in the frameworks used. Whilst the development of intelligent medical systems is still an intensive research area, parts of this intelligence are implemented in low-resource processing platforms. This is driven by an explosion of data volume, because in order for pervasive sensing to be sustainable for managing large population groups, it is necessary to reduce the data at source through effective *on-node processing*. To this end, the mapping of analytical algorithms directly to *ultra-low power* μC (microcontrollers) and implantable sensors has been pursued. Musiani et al. [83] argued that a signal analysis based on a Hilbert transform implemented in a Shimmer programmable sensor [84] node required over 100 MIPS (million instructions per second). Common operations used in machine learning and signal processing such as matrix inversions and decompositions, have a complexity order of approximately $O(n^3)$. This means that for just 100 samples, a simple algebraic operation would

require around 1 million internal loop instructions, without accounting for additional operator instructions such as floating point products. Nevertheless, simple and *light-weight processes* have been implemented for elemental processing parts of online algorithms such as noise filters, feature extraction and peak detectors.. For instance, in Hulzink et al [85] a continuous wavelet transform based algorithm is implemented on-board in an ad-hoc low-resource integrated platform that enables running pre-compiled C scripts to detect ECG heartbeats. For the recognition of physiological activities, some studies have proposed to reduce the on-node implementation to the inference process of a pre-trained model [86].

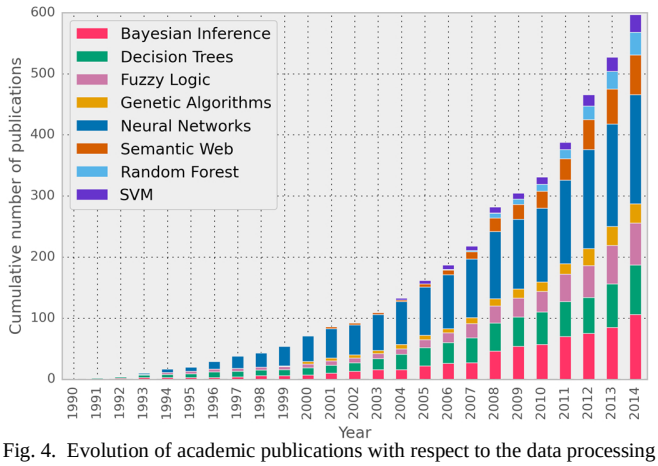

Fig. 4. Evolution of academic publications with respect to the data processing frameworks used to develop clinical decision support systems. Publication data were collected from the following databases: IEEE Explorer, ACM Digital library, PubMed (National Library of Medicine, Bethesda, MD), Web of Science and Scopus.

Concurrent advances in *high-performance computing* have made it possible to process high volumes of data in large repositories more efficiently. In particular, map-reduce frameworks with sophisticated models of data caching and in-memory processing have played a key role from a software viewpoint. Likewise, advances in hardware including co-processors and GPU accelerators such as Xeon Phi and Nvidia Tesla have enabled highly intensive operations and transformations to be performed in parallel. Machine learning algorithms that have benefited from these advances include *deep learning*, which can also be used to learn a set of artificially generated features. *Ensemble learning* is another interesting framework aimed at combining inferences from many algorithms trained with subsets of the data via a voting strategy, which can run as parallel processes.

G. Machine Learning

Continuous sensing data in real-life environment is beset with artifact, missing data and uncertainties. *Bayesian estimation* provides an intuitive and formal foundation to express learning models in terms of uncertainty. For this reason, graphical models based on hierarchical and non-hierarchical Bayesian networks (BN) have become popular in clinical research. The inclusion of temporal data has raised interest in Dynamic Bayesian Networks (DBN), which were previously more commonly applied to areas such as robotics, sensing and speech recognition. To obtain an inference based on multiple sources and therefore a large amount of heterogeneous dimensions, models able to integrate the conditional dependencies and relationships between these factors are appealing. Thus, in clinical applications, causal modelling has been suggested as a method to facilitate the specification of BNs with many parent variables [96]. When the purpose is to model the causality of concurrent dynamical systems in continuous time, learning probabilistic graphical models considering all unmeasured confounding factors can become challenging, but the availability of continuous (rather than episodic) context-aware sensing data offers unique opportunities to address this issue.

Instead of using probabilities, *fuzzy logic* is a framework that is based on the concept of "degree of truth". *Fuzzy set* memberships enable the input to interpolate between the crisp set of classical logic, allowing a soft transition of the degree from false to true. These soft assumptions are helpful as they allow formalising vagueness in the inference of clinical decision support systems. In order to model uncertainty, general type-2 fuzzy sets implement the same operators as type-1 fuzzy sets but the membership function is made three-dimensional, therefore enabling to account for uncertainty in

TABLE II
EXEMPLAR TECHNOLOGIES FOR THE FIVE V'S OF BIG DATA IN PERVASIVE HEALTH

	Causes	Technological solutions	Relevant research areas
Volume	▪ Large population and biological datasets. ▪ Growing streaming data.	▪ Large-scale processing frameworks. ▪ Scalable and flexible data storage.	▪ Map-reduce (in-memory) frameworks.[87] ▪ Scalable distributed databases and cloud computing. [87]
Velocity	▪ Continuous streaming data. ▪ High frequency data sources (*e.g.* pervasive sensors, social media).	▪ Light-weight processing models. ▪ High performance computing (HPC).	▪ Low-complexity algorithms, very fast machine learning and on-node processing. [88] ▪ Grid computing, parallel programming and coprocessors. [87]
Variety	▪ Integration of multiple health sources. ▪ Distinct labelling strategies across institutions.	▪ Metadata protocols. ▪ Semantic web models of data integration.	▪ Non-relational databases. [89] ▪ Formal ontologies and semantic web. [90] ▪ Multi-agent systems. [91]
Veracity	▪ Measurement imprecision, confounding factors. ▪ Inference certitude of output.	▪ Uncertainty quantification. ▪ Causality.	▪ Uncertainty analysis (Bayesian probabilities or fuzzy sets). [92] ▪ Causal modelling. [93]
Variability	▪ Non-stationary systems. ▪ Unforeseen events in health. ▪ Seasonality and behavioural changes.	▪ Adaptation. ▪ Handling concept drift.	▪ Online learning models. [94] ▪ Adaptive and drift-aware learning models. [95]

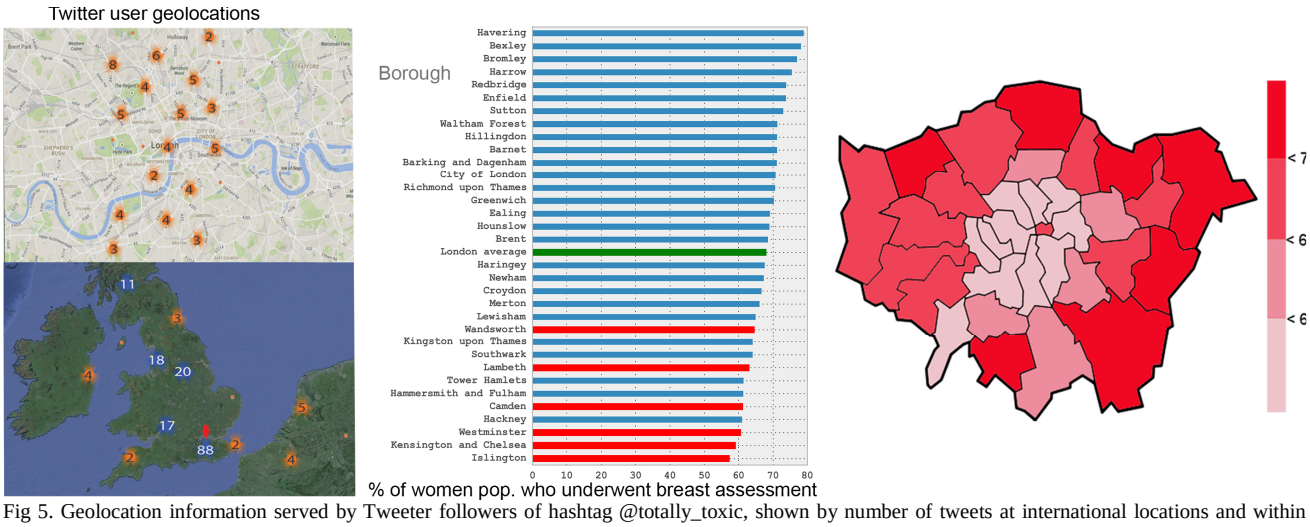

Fig 5. Geolocation information served by Tweeter followers of hashtag @totally_toxic, shown by number of tweets at international locations and within London (left); percentage of women who underwent breast assessment in the last three years by London borough of residence (middle); map of London boroughs coloured by breast assessment percentage in women population (right).

the primary membership. Fuzzy systems have been widely applied to the first [97, 98] and second-generation applications of pervasive health [99]. Soft-clustering algorithms based on fuzzy logic have been proposed as a method to scale data analysis to large volumes of data [100]. *Data stream learning* techniques have been proposed to process the data one-pass and enable adaptation [101]. More recently, similar data stream learning algorithms have been developed using different frameworks [102].

H. From Sensor Informatics to Big Data

One of the bottlenecks to consider for the third generation of pervasive sensing platforms is to achieve rapid and scalable processing for large datasets. From a software point of view, processing big data is usually linked to programming paradigms such as maps reduce [103]. Several open-source frameworks such as Hadoop are frequently used to store a distributed database in a scalable architecture, as a basis for tools (such as Cascading, Pig, Hive) that enable developing applications to process vast amounts of data (by the order of terabytes) on commodity clusters. However, when combined with continuous streams of pervasive heath monitoring this also requires capacities for iterative and low-latency computations, which depends on sophisticated models of data caching and in-memory computation. Thus, other frameworks such as Storm and Spark have been created to fulfil this gap.

For handling data variety and heterogeneity, s*ematic web technologies* such as ontologies and data representation languages are used. They provide structural and organisational tools of knowledge-management, already adopted by many organisations [104]. Defining explicit data descriptors and semantics can have multiple uses such as reasoning, integrating heterogeneous sources, data linkages and data sharing. Linking data is a particularly important feature to provide new sensing applications with querying capabilities over the multiple sources for exploration and synthesis.

One of the common issues in sensing data is to deal with unforeseen events in health such as seasonal and behavioural changes. Some data stream algorithms have been implemented considering adaptation such as adaptive, very fast decision tree learners [105], which has been used for sleep apnoea monitoring [106]. Likewise, an adaptive neuro-fuzzy stream learning approach was proposed for the recognition of activities of daily living [107, 108]. Additionally, signal processing algorithms such as symbolic aggregate approximation can also implement adaptation to deal with data stream segmentation and approximation [109]. Adaptive stream data algorithms can be made *resource-aware* by taking advantages of their adaptation and online processing capabilities to leverage their control parameters and minimise the amount of input/output data processed [110].

The above considerations can be mapped to the 5 Vs considered in big data research as listed in Table II. Regardless of the 5 Vs, almost all pervasive health applications raise privacy challenges. For big data applications, the issue is greater due to the need for performing linkages with other sources. This requires the use of identifiers that uniquely represent the data about an individual. The techniques for data privacy preserving analysis can be categorised into five groups: 1) encrypting data, *i.e.* cryptographic; 2) adding noise to data, *i.e.* randomised responses; 3) grouping data by factor/attribute, *i.e.* condensation; 4) hiding attributes in data, *i.e.* anonymisation; and 5) applying a transformation in the factors/attributes so that the data distributions are recovered independently, *i.e.* perturbation. In addition, pervasive sensing data can also raise security threats across the different stages of data transmission from sensors to remote databases. Sensor biometrics have been proposed as a solution to secure communications in body sensor networks [111].

IV. Implication on Future Healthcare Delivery

The developed world is experiencing a major demographic shift. Age-related diseases, such as cardiovascular disease, cerebrovascular accidents and cancer are set to become more prevalent [112]. Emerging evidence suggests rising ill-health in the elderly population with an increasing incidence of chronic conditions such as osteoarthritis, chronic airways disease and diabetes [113]. Similarly, the global burden of

disease is leading to an increase in interventional procedures, especially surgery [114]. Whilst techniques have become increasingly minimally invasive, post-operative complications such as surgical site infection, inadequate tissue healing and gastrointestinal anastomotic failure persist.

Traditional monitoring of chronic diseases and even acute symptoms reflects the episodic nature of the symptomatology. However, pathology is a continuing process and certain transient but important events may go undetected with such infrequent measurements. Despite the ability to measure extensive biomechanical and biochemical information, the diagnostic and monitoring utility is generally limited to brief time points and unrepresentative physiological states or artificially introduced tests. Transient critical abnormalities cannot always be captured, leading to delayed diagnoses and escalating healthcare costs. Important and even life-threatening disorders can go undetected because they occur infrequently and only under specific situations so that they may not be recorded objectively. Pervasive sensors that provide continuous physiological monitoring offer new hope for complex data analysis, leading to physician alerts to support clinical decision-making and diagnosis.

One good example of smart sensing combined with the integration of a diverse range of data sources is to revisit the recent PIP implant scandal as previously mentioned. As an example of the way in which third-generation systems may change the way health crises are anticipated and managed by public health authorities. PIP breast prostheses with a significantly higher risk of rupture and comprising lower levels of platinum and higher levels of low molecular weight siloxanes than medical grade silicone were implanted into thousands of women worldwide. Many women presented themselves to clinics describing pain, swelling, tenderness and lymphadenopathy associated with symptomatic implant rupture. Asymptomatic women attended requesting ultrasound scans to check the integrity of their implants. Others attended unsure if PIP implants had been inserted. Whilst robust evidence of a link between PIP rupture and disease is lacking, many attribute rupture to autoimmune diseases that were subsequently contracted. A recent review by the department of health has called for a new implant register [115] and greater regulation but currently there is no way of monitoring implant integrity without clinical assessment.

Analysis of social media has revealed locations where the social interest regarding faulty breast prostheses is highly prevalent. Analysing the current administrative database offered by the National Health Service (NHS), we evaluated the number of women in London who underwent breast assessment during the last three years and classified them by the borough of residence as shown in Figure 5. These data may suggest that women at risk due to their exposure to PIP do not reside in areas with easy access to breast screening assessment centres. These data could be combined in an inference system to identify the geo-location of women affected based on social networking trends, and determine the likely volume of patient's requiring assessment and treatment to aid workforce planning and streamline resources to locations of greatest need.

It is interesting to note that with this information alone, a health alarm could have been triggered. Against this background of heightened awareness and concerns regarding implant ruptures, next generation of wireless low power, low drift sensors incorporated into the elastomer that monitor outer shell integrity and / or that sense silicone on the outer surface of the implant that may herald an intracapsular rupture. Automated detection of rupture is coupled with an alert sent to the surgeon who implanted the device. The implant is removed at the earliest opportunity, silicone spillage into body tissues is contained and capsule formation minimised.

A. From Episodic Monitoring to Continuous Sensing and Integrated Care

The devices listed in Table I represent the general trend from episodic monitoring to continuous sensing and integrated care. Accurate and timely detection of healthcare states facilitates early treatment, limits body trauma and prevents organ damage. The negative impact of episodic data capture in healthcare is arguably best exemplified in the management of cardiovascular disease, post-operative surgical care, monitoring of tissue healing and in cancer treatments. Following myocardial infarcts, life-threating arrhythmias can occur unpredictably without warning, and may remain undetected if cardiac monitoring is infrequent and intermittent. Sensors have already been developed for accurate methods for continuous monitoring of blood pressure, pulse and cardiac rhythm [116] such that arrhythmias can be detected in near real time and signals sent to a smartphone for ulterior processing [117]. Critical abnormalities of cardiac rhythm such as atrial fibrillation can be detected, recorded and rapidly treated.

For monitoring post-operative issues such as sepsis [118], for example, there are data to suggest that aggressive early therapy can improve outcomes. Surgical site infections, dehiscence of wounds and gastrointestinal anastomosis are recognised complications following surgery. The severity of these complications can be mild necessitating oral antibiotic therapy and close observation in hospital but can be serious with life-threatening sepsis necessitating repeated surgical and radiological interventions with high morbidity and mortality. Hospital stay is inevitably prolonged, significantly inflating the costs of healthcare delivery. Early detection of surgical site infections, dehiscence and anastomotic failure are critical to patient management to ensure prompt instigation of appropriate therapy and to avoid the mortality associated with overwhelming sepsis, and yet in current clinical practice these complications tend to be detected far too late. Wound infection is self-evident once the patient has developed erythema, pain, tenderness or is discharging pus from the wound. By the time important changes are detectable within the patient's circulation, pathological processes have, by definition, reached a systemic level and are likely to challenge the patient's physiological reserve. Sensors built into dressings, embedded within catheters and anastomoses such as those that can detect biochemical changes in the microenvironment (e.g. lactate, glucose, pH) may herald SSI or tissue failure, prompt further investigation or corrective clinical action.

It has been shown repeatedly that delayed diagnosis negatively impacts cancer outcomes, whereas screening saves lives [119]. Similarly, the episodic macroscopic and structural

imaging of tumours in patients undergoing neoadjuvant chemotherapy means that assessments of tumour response remains crude. Smart sensors implanted within the radiological marker clips, capable of monitoring at the cellular level and/or continually detecting cellular proliferation proteins may provide a more accurate assessment of chemotherapeutic response upon which clinicians may act to switch regimen or expedite surgery in case of poor response.

The above examples illustrate that a vast amount of clinical information is recorded on any given patient and the attending clinician may not always have easy access to this data, impairing quality of care. Patients with increasingly complex health and social needs often visit a number of healthcare providers, who may recommend treatments in sequence or in parallel without understanding the impact on the holistic needs of the patient. Continuous sensing may provide a convenient solution to the need for *integrated care* which describes a drive towards a patient-centred, co-ordinated and tailored service. For example, a cardiologist may prescribe a statin for a patient with hypertension and hypercholesterolaemia without realising they were taken off this treatment previously as it was causing severe cramps. The result is unnecessary readmissions and costs. The next generation of sensing may have the capability to minimise these vicious cycles of poor care by improving awareness of medication side effects (knowledge) and enhancing linkage between healthcare providers through rapid knowledge and event sharing (integration).

B. *Stratified Patient Management*

Clinical decision support systems able to digest and understand continuous personalised health data in real-time can improve the quality of care provision particularly in the field of cancer management. Clinical decision support systems have the advantage of being able to capitalise on a broad knowledge-base by data mining patient records and accounting for other data repositories such as genomics, clinical phenotypes and bio-markers. The clinical impact of clinical decision support systems is best exemplified by considering the management of a patient treated for malignancy. Consider a patient scheduled to receive chemotherapy for bladder cancer. The patient's DNA is sequenced, identifying a high-risk genotype for urological malignancy and an appointment is scheduled with a geneticist to discuss the impact of the risk mutation. The clinical team suggest a wearable system for constant physiological monitoring, being able to detect poorly controlled hypertension and consider increasing blood pressure control.

Following the first cycle of chemotherapy, the wearable sensor detects a pyrexia (body temperature > 37.6^{o} C) and a low neutrophil count. This information can be used to identify likely side effect of chemotherapy. Once chemotherapy has been discontinued and clinical remission established, the system seeks to promote health and wellbeing and minimise disease recurrence. For example, wearable motion sensors can detect sedentary behaviour and a recommendation can be sent to the patient to engage in a more active lifestyle.

C. *Managing the Continuum of Health and Disease*

With the current paradigm shift towards prevention, prediction, personalised treatment and participatory medicine, it is necessary to consider health and disease as a continuum. For many life-style diseases, enhancing pervasive health systems with context-aware capabilities provides an extra set of contextual information about the monitored condition under consideration. For example, motion sensors combined with intelligent behaviour modification can be used to motivate overweight and obese individuals engage in physical activity to lose weight improving diabetic control, hypertension and reducing the risk of cancer [120]. Sensors that monitor basal metabolic rate and activity energy consumption can derive total energy expenditure. However, weight loss only occurs if total energy expenditure exceeds calorific intake and accurately calculating the latter can be challenging. Therefore, there is a need for sensors that can monitor both calorific intake and energy expenditure simultaneously and feedback data to the user logs of consumption and activity.

Similarly, shifts toward prevention, predication and more personalised approaches are required to improve outcomes in major non-communicable diseases such as cancer. Traditionally, cancer management had relied on generic treatments supported by trial data such that any two patients with a given cancer may be similarly treated on the basis that they were found to have contracted the same 'disease'. Yet, a critical aspect of most complex diseases such as cancer is that they encompass many different types of disease owing to differences in disease-perturbed networks [121]. Returning to the example to breast cancer, data from recent genomic analysis informs us that the phenotypic diversity of breast tumours is supported by similar diversity in gene expression resulting in an improved molecular taxonomy of breast cancer [122]. Improved risk modelling and identification of at risk mutations will lead to more widespread adoption of preventative strategies (e.g. risk screening, chemoprophylaxis and risk reducing surgical protocols). Moreover, improved genetic stratification of cancer may enable the pharmaceutical industry to develop novel drug targets. Routine collection of genomic, metabonomic and proteomic data in patients with cancer, if coupled with sensor informatics has, the potential to improve our understanding of resistance to chemotherapeutics. The future of personalised cancer treatments demands this improved understanding of drug choice, dose and duration to enhance cure, minimise adverse effects and treatment failure, and prevent recurrence.

V. Discussion and Conclusions

Over the last decade, technological advances have supported the evolution of a pervasive health paradigm, which is also captured in alternative names such as *ubiquitous health* (u-health) and *mobile health* (m-health). Considered in this paper we discussed different generations of devices and their associated analytics.

From a clinical perspective, the evolution of each generation of pervasive health monitoring has consisted of a sequence of technological steps necessary to provide integrated care, bridging the gap between health and disease management. Current healthcare services are typically

fragmented into many processes that are often disjoint in space and time.

From a technical standpoint, there remains a need for horizontal advances within each generation to improve the quality of the involved technologies. However, vertical developments may see an entirely new generation of wearable sensing devices and smart implants that are low power, low drift, resistant to biofouling and that can be easily implanted and extracted when no longer required.

From a data analysis perspective, long-term continuous sensing and the need not only to monitor but also to intervene in real-time brings unique challenges, as well as opportunities to sensor informatics. Other challenges are related to integrating large data sets from heterogeneous health data sources. Advances in high-performance computing, stream learning models and semantic web are therefore likely to play a key role in the future. These technical challenges, if overcome, are set to transform future healthcare delivery. Big data mining and social network analysis have the potential to manage global epidemics such as Ebola, incorporating geographical information systems to track cases, accelerate warning systems and streamline outbreak response [82]. This can be translated into clinical medicine progress from a reactive to a proactive discipline. In our opinion, meeting these challenges will help address key areas of unmet clinical needs including management of chronic diseases such as diabetes and cancer, detection of nosocomial and surgical site infections and monitoring of surgical prostheses. More importantly, technological advances in sensor design coupled to improved data analytics will shift the focus from disease to prediction and prevention. Predictive medicine must capitalise on diverse information from a range of bioinformatics data to define a baseline of health (wellness) and then similarly employed to detect transition to disease. Mining these numerous data sources per individual will help create predictive and actionable models [121] to better tailor therapeutic regimens thereby improving outcomes and quality of life. Challenges such as data storage, analytics, and a cultural reluctance to rely on open-source algorithms, data sharing and open data policies will need to be overcome.

Clearly, if the ultimate goal in healthcare is to be based on preventative, predictive, personalised and participatory medicine, the sensing technologies as discussed in this paper and their future evolution will play a key role in realising this goal.

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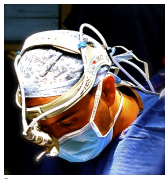

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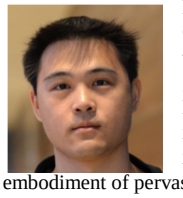

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