Industry 4.0 and Health: Internet of Things, Big Data, and Cloud Computing for *Healthcare 4.0*

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***Abstract*—Industry 4.0 and its main enabling information and communication technologies are completely changing both services and production worlds. This is especially true for the health domain, where the Internet of Things, Cloud and Fog Computing, and Big Data technologies are revolutionizing eHealth and its whole ecosystem, moving it towards *Healthcare 4.0*. By selectively analyzing the literature, we systematically survey how the adoption of the above-mentioned Industry 4.0 technologies (and their integration) applied to the health domain is changing the way to provide traditional services and products. In this paper, we provide (i) a description of the main *technologies and paradigms* in relation to Healthcare 4.0 and discuss (ii) their main *application scenarios*; we then provide an analysis of (iii) carried *benefits* and (iv) novel *cross-disciplinary challenges*; finally, we extract (v) the *lessons learned*.**

I. Introduction

The growth of world population and the rising expectations for effective treatments and overall better quality of life are putting increasing pressure on healthcare. Therefore, healthcare keeps being one of the most important social and economic challenges worldwide, asking for new and more advanced solutions from science and technology [1, 2]. In response to such needs, since the early 1990s, the Information and Communication Technologies (ICTs) have positively impacted the access, the efficiency, the quality of virtually any process related to the healthcare [3]. Hence, the expression *eHealth*, intended as the application of ICTs to healthcare, has become of common use. Indeed, eHealth has attracted great public and private interest and fostered unprecedented levels of investment in terms of both research effort and funding [4].

As the founding technologies evolve, also eHealth is following along, therefore the specific characterization of the term has undergone progressive changes and specifications [5], the most recent ones regarding the paradigm known as *Industry 4.0* (hereafter also "*I4.0*"). In its broader meaning, the concept of I4.0 can be seen as a governmental explicit commitment to foster a set of technologies and the cultural and legal framework necessary to harness their full potential. The term itself is tracked back to November 2011, in an article by the German government defining its high-tech strategy, named "Industrie 4.0", for 2020 [6]. Besides the technologies involved, there are in fact also development plans including aspects of enterprise management and work organization, regulatory frameworks, and dissemination and training. From the strictly technical point of view, this so-called *fourth industrial revolution* is based mainly on the concept of *Cyber-Physical Systems* or CPS (integration of computing, communication, and control), and heavily relies on three groups of technologies (*pillars*): the *Internet of Things* (IoT) paradigm (characterized by the pervasive presence of a variety of uniquely addressable cooperating objects such as mobile phones, sensors, and actuators); *Cloud and Fog Computing* (providing virtually unlimited computing, storage, and communication resources as utilities, i.e. on-demand and pay-per-use); *Big Data Analytics* (to extract value from challenging amounts of data).

The evidence of the rapid and pressing technological evolution—joint with the worldwide rising governmental efforts—leads to the conclusion that the healthcare sector is already facing the impact of I4.0, effectively moving *eHealth* towards *Healthcare 4.0* (henceforth also "*HC4.0*"). Although the term *Smart Health* is often adopted with different acceptation to generally refer to the adoption ICT-based healthcare solutions, it is worth noting that the paradigm we define here as Healthcare 4.0 has its own peculiarities. Indeed, in the scientific literature several definitions for Smart Health can be found ranging from "the medical and public health practice supported by smart mobile devices (i.e. smart-phones)" [7] , or "the intelligent health management and medical service using information technology" [8], to "the use of technologies such as smart mobiles, smart cards, robots, sensors, and tele-health systems via Internet on pay-per-use basis for best medical practices" [9]. Healthcare 4.0 is instead deeply characterized by the adoption of three main paradigms: the Internet of Things, Big Data, and Cloud Computing that together are revolutionizing eHealth and its whole ecosystem, like Industry 4.0 is doing for the manufacturing sector [10]. The intrinsic multi-disciplinary nature of Healthcare 4.0 makes it harder and harder for the operators and stakeholders in this field to keep the pace with technological progress. While several introductions and surveys exist regarding either the technologies at the basis of Industry 4.0, or single ICT applications to healthcare (eHealth) [11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21], we found a lack of an up-to-date work focusing on the aspects most relevant to Healthcare 4.0. Therefore, with this paper we aim at introducing the technological aspects at the basis of the ongoing industrial revolution as applied or applicable to healthcare, to shed light on their use and deepen their understanding. This way, we provide for specialists in some of the involved fields also an overview of the others, fostering the cross-disciplinary interactions at the basis of HC4.0.

We adopted a systematic approach in exploring the literature, following the methodology described in [22]. For the aims and scope of our paper, the identified keywords have been: "e-health", "healthcare", "cloud computing", "Fog Computing", "Iot", "Internet of Things", "Big Data". As research engine Google Scholar has been selected, to avoid bias on publishers according to best practice. From the +800 results we selected an initial set of 80 papers for the snowballing methodology, using the following criteria: paper written in English, full text available either publicly or by subscription by University of Napoli Federico II, then based on relevance of title and highest number of citations. By applying the backward and forward snowballing process, considering the abstract for relevance and for papers candidate to inclusion also the full paper, we obtained a set of 160 papers. These have been organized in sections pertaining to the technological Pillars. Both generic and specific suggestions by the anonymous reviewers for expanding the resulting set have been also evaluated and included, leading to a final total of 171 papers.

Our contribution is fivefold: (i) we introduce the I4.0 pillars highlighting their properties more relevant to healthcare, characterizing the HC4.0; (ii) we review the state-of-art application scenarios of HC4.0; we discuss (iii) the main benefits and (iv) the main challenges deriving from the advent of HC4.0; (v) we draw lessons learned.

This paper is structured as follows. We briefly describe each pillar to the depth necessary to appreciate its contribution to HC4.0 in Section II. Then we review all the main application scenarios enabled by HC4.0 in Section III. We highlight and discuss the main benefits and challenges of the ICT pillars for HC4.0 in Section IV, also considering the point of view of patients and healthcare professionals. In Section V we extract the lessons learned through our study. Finally Section VI draws the conclusions.

II. ICT pillars for Healthcare 4.0

Today's world is being transformed by the availability of *anywhere-and-anytime connectivity*. The unprecedented ubiquitous presence of wireless and mobile technologies also in developing countries, the availability of low-cost, miniaturized wireless sensors, as well as the cost-efficient services provided by new hardware infrastructures (e.g., huge-scale datacenters leveraging virtualization technologies) have enabled new healthcare services, or new levels of quality and cost-efficiency in established ones. Examples go from the rising availability and quality of medical software applications—also as *mobile apps*—driven by the integration of mobile devices into clinical practice [23], to backing people suffering from obesity or chronic diseases as well as aging population [15] by means of large-scale analysis of massive digitized data [5, 21]. A sign of the radical change in medicine enabled by these new technologies can be found in the concept of *P4 Medicine* [24], i.e. *predictive*, *preventive*, *personalized* and *participatory*. This approach—based on a comprehensive understanding of each patient's own biology instead of clustering patients into treatment groups—is being applied to significantly reduce global health budgets, e.g. by reducing hospitalization and by minimizing the unnecessary or inappropriate use of drugs and procedures [25, 26]. These innovations all come from the broad set of ICTs, and among them in this section we will focus on three fundamental enablers, that we dub *pillars* of HC4.0 for their importance: IoT, Cloud Computing, and Big Data, by detailing the use of these technologies in the field of healthcare. Their growth in terms of academic interest and production is shown in Fig. 1. We acknowledge that other aspects, both technological and not, can be considered in relation with HC4.0, but compared with the pillars above, they are either secondary or are supported by technologies at a lower degree of maturity. Among these, the 5G ecosystem [27]—whose specifications and technical solutions are still being defined and are under extensive discussion—undoubtedly plays a major role. Indeed, the advantages of these emerging technologies (e.g., near-zero latency, advanced quality-of-service capabilities, and data rates on the order of Gbps), are expected to bring multiple benefits to fuel the broad expansion of health solutions [28].

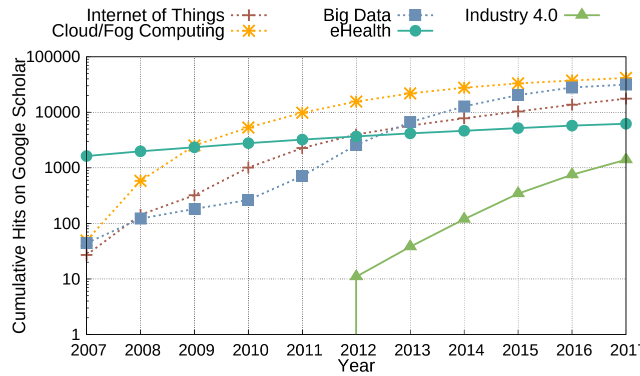

Figure 1: Popularity in the scientific literature of HC4.0 pillars (number of publications per year). Data source: *Google Scholar* (exact match in title).

A. Internet of Things in HC4.0

A general vision of the IoT is presented by ITU as the move from *anytime, anyplace connectivity for anyone*, forward to *connectivity for anything*, initially with focus on digital identification and machine-to-machine (M2M) communications [11]. The objects conforming to the IoT have a wide range of understandings and connotations, including RFID [29] and Wireless Sensor Networks (WSNs) [30] and all share some set of strict requirements in terms e.g. of size, power consumption, processing capabilities. Of specific interest for healthcare, Wireless Body Area Networks (WBANs) are composed by wireless devices (sensors and actuators) attached on or implanted in the human body [15, 31].

Due to such complex and heterogeneous scenario, IoT-related topics are often addressed referencing different logical layers [32], i.e.—from bottom to top: (i) *perception layer* (made up of sensors and actuators); (ii) *transmission layer* (conveying sensed information to the upper layers); (iii) *computation layer* (in charge of processing data and taking decisions); (iv) *application layer* (using of the IoT infrastructure for high-level goals such as healthcare, home automation, transport, manufacturing, etc.). Most of the academic and industrial research on IoT has focused on the *transmission layer* and its communication protocols. Although designing and implementing a *low-power*, *highly reliable*, and *Internet-enabled* communication stack is a commonly agreed requirement, IoT definition still appears somehow fuzzy for some aspects. We refer to [33] and [34] for a detailed discussion on standards as well as related challenges and opportunities.

The most recent vision of IoT, when applied to industry (e.g., manufacturing processes), greatly overlaps with I4.0. This can be in fact considered as a step beyond IoT, either adding reference architectures with logistic and manufacturing details [35], or conversely adding IoT technologies to already automated processes, with a number of new opportunities (and challenges) as a consequence [36]. Healthcare proved to be among the most attractive areas for IoT application [14, 37]. The success of this paradigm is reshaping modern healthcare, with promising technological, economic, and social prospects: IoT is arguably the main enabler for distributed healthcare applications [38], thus giving a significant contribute to the overall decrease of healthcare costs while increasing the health outcomes, although behavioral changes of the stakeholders in the system are needed [38, 39]. Progress in wireless technologies with related performance improvements heavily supports real-time monitoring of physiological parameters, thus easing the uninterrupted care of chronic diseases, allowing early diagnoses, and the management of medical emergencies [14]. In this context, medical, diagnostic, and imaging sensor devices are central for fruitfully leveraging IoT in the health domain [14, 40]. However, a huge number of applications also take advantage of general-purpose smart devices (PDAs, tablets, and smartphones) [14, 41, 42].

For instance, IoT enables scenarios where smart devices interact with other smart objects in order to gain new knowledge and awareness about both users and the environment for supporting decision [43]. Inspired by the prime IoT paradigm, a number of variations have been derived in the health field, each with its peculiarities (see Tab. I). The *Wearable Internet of Things* (*WIoT*) [44] intends to implement telehealth to achieve an ecosystem for automated interventions. Leveraging body-worn sensors, WIoT enables monitoring data useful in enhancing individuals' everyday quality of life (e.g., focusing on factors such as behaviors, wellness, habits, etc.) and connects patients to medical infrastructures. The *Internet of Health Things* (*IoHT*) is based on the combination of mobile apps, wearables, and other connected devices and leverages context-aware *always-on* professional-grade sensor medical devices [41]. The *Internet of Medical Things* (IoMT) [45] refers to applications consisting of implantable and wearable devices connected to a personal a smartphone or a smartwatch that is connected to the Internet and acting as personal hub. The *Internet of Nano Things* (*IoNT*) [2] refers to the application of IoT in nanomedicine, to implement more personalized monitoring, diagnostics, and treatment to implement proactive monitoring, preventive health, chronic care disease management, and follow-up care. The *Internet of mobile-health Things* (*m-IoT*) [46] envisions a connectivity model between low-power personal-area networks and evolving 4G networks, emphasizing the existing specific features intrinsic to the global mobility of participating entities.

B. Cloud and Fog Computing in HC4.0

"Cloud Computing" (or simply "Cloud") is a paradigm that enables "Utility Computing", i.e. the leasing of computing resources (computational power, storage, and the related networking resources) in real time, with minimal interaction with the provider. This way, Cloud simplifies operation, as it does not require a careful dimensioning and forecast of needed resources, allowing pay-per-use billing on a short-term basis, without upfront commitment by the user. Moreover, cloud customers take advantage of apparently infinite resources on demand, and are able to either leverage or deliver *everything as-a-service*: the most common services are characterized as Infrastructure, Platform, or Software as-a-Service (IaaS, PaaS, and SaaS, respectively) [47], with further variations such as Function-as-a-Service (also dubbed "Serverless Computing" [48]). Notably, Cloud is necessary to satisfy a number of needs deriving from IoT [37], to the extent that, according to some visions, it is intended as one of the IoT upper layers [49, 32]. The occurring migration to cloud services is fueled by a trend emerging in the last decade: i.e., the extension of functionalities embedded in field devices that has endowed them with more *intelligence* and flexibility, thus allowing to move some functions to the Cloud [50], with the related scalability and responsiveness (and eventually, economic) gains.

IoT Paradigm		Year	Ref.
Internet of Medical Things	(IoMT)	2017	[45]
Internet of Health Things	(IoHT)	2016	[41]
Internet of Nano Things	(IoNT)	2015	[2]
Wearable Internet of Things	(WIoT)	2014	[44]
Internet of m-health Things	(m-IoT)	2011	[46]

Table I: Internet of Things paradigms in Healthcare.

Figure 2: Main drivers to the adoption of Cloud Computing in Healthcare (percentage of motivations reported in surveyed papers).

However, several shortcomings of the Cloud Computing paradigm have become apparent over the years, mostly related with the communication between the end device and the datacenter hosting the cloud services: latency, bandwidth, cost, and availability of the connection all contribute to limit a number of uses for Cloud Computing. The proliferation of pervasive mobile devices further worsened this phenomenon, highly challenging the Cloud paradigm. Indeed, in several contexts the Cloud cannot meet all the requirements of many applications—specifically, for healthcare—surfacing the need for a different architecture [51]. Different concepts, terms, and expressions have been coined for the solutions proposed as detailed in the following. *Fog computing* [52] proposes to transfer some cloud computing services to the edge network, close to user devices and possibly partially relying also on users' device resources, thus distributing the load between end devices and traditional cloud datacenters and bringing, among others, local-term security, low-latency rates and faster responsiveness, while helping to improve performance scalability to the whole system.

In fact, fog computing enhances on-time service delivery and significantly mitigates a number of issues related with cloud such as cost overheads, delay, and jitter while information is transferred to the cloud [53].

It also supports user mobility, resource and interface heterogeneity, and distributed data analytics to address the requirements of distributed applications requiring low latency. Moreover, it simplifies the management and programming of computing, storage, and networking services between datacenters and end devices [54]. Therefore, Fog computing is a powerful tool to support the decentralized and intelligent processing of unprecedented data volumes generated by IoT sensors deployed to integrate physical and cyber environments, thus helping the IoT reach its vast potential.

When clients are mobile nodes and the computing capabilities are moved to the radio access network, this concept specializes as *mobile edge computing* (proposed ETSI standard [55]). *Mobile Cloud* has been proposed as umbrella term [56], including the following scenarios: (i) applications are run on (resources-rich) remote servers, with the mobile devices being the (thin) clients; (ii) mobile devices are used as resource providers for the Cloud, in a mobile peer-to-peer network; (iii) mobile devices offload their workload to a (local) edge cloud. In this context the idea of *cloudlet* was developed by the Carnegie Mellon University [57], referring to a middle tier (between the mobile device and the traditional Cloud): the cloudlet is a self-managed "datacenter in a box", a mini-cloud with resources sufficient to host workloads for a handful of (mobile) users concurrently. Cloud Computing is indirectly implied in the other pillars of HC4.0, namely Big Data and IoT, but also for Visual/Virtual Computing and other healthcare applications.

The characteristic benefits of Cloud Computing in containing integration costs and optimizing resources are specifically significant in the healthcare scenario. Cloud Computing meets the IT needs of the healthcare sector to simplify health processes [18, 16, 5, 58], facilitate the adoption of healthcare best practices, and inspire and foster more innovations [9]. The adoption of Cloud technologies in the context of healthcare has been dubbed *Healthcare as a Service (HaaS)* [59, 47]. Compared with the common drivers to the adoption of Cloud technologies in more general applications and in the IoT paradigm [37], HaaS applications share the same benefits from scalable, on-demand, and virtually infinite computation, storage, and networking resources; in addition to these, other aspects have been found to be important, such as: ease of data sharing, ease of data collection and integration, and in some cases enhanced performance, availability, reliability and security [60, 61, 62, 63] (see Fig. 2). Moreover the technologies related to mobile and personal devices benefit from Cloud and Fog Computing for managing the growth in digital data and *anywhere-and-anytime* request for medical services [16, 64, 37]. Specific contributions to the healthcare sector regard the overall improvement of the quality of service: when many *smart devices and objects* are the more and more part of everyday's life of patients and physicians, availability and communication latency can be serious issues, affecting predictability, delaying decision processes, and potentially compromising the delivery of healthcare services [65, 66]. Mobile cloud mitigates or solves these issues and also provides systems with contextual information, allowing for more user-friendly and personalized services and adaptive quality of service management [56]. Summing up, Cloud, Fog and Mobile Edge Computing constitute a big part of HC4.0, with positive impacts on both healthcare research and services improvement (enhancing quality, making them affordable for a bigger set of people than currently possible, and enhancing the outcomes for patients).

C. Big Data in HC4.0

The expression *Big Data* has a much discussed scope and definition. Over time, its focus has moved from datasets characteristics in relation to the *current* technologies (datasets which could not be captured, managed, and processed by general computers within an acceptable scope, according to Apache Hadoop definition) to the technologies designed to economically extract *value* from *very large volumes* of a *wide variety* of data, by enabling the *high-velocity* capture, discovery, or analysis [67]. A commonly agreed and concise characterization based on five Vs captures the largest and most cited common set of properties associated with Big Data: (i) *Volume* (data scale increases); (ii) *Velocity* (collection and analysis are subject to time bounds); (iii) *Variety* (data is composed of various types, i.e. structured data, unstructured, and semi-structured); (iv) *Veracity* (data has varying degrees of trustworthiness, according to provenance, management, and processing); (v) *Value* (the whole architecture is aimed at—economical—value extraction). This 5-V characterization highlights the strong context-dependent nature of Big Data, that is so defined necessarily with reference to specific applications (Value) and technical constraints (Volume, Velocity, Variety, Veracity). These peculiar requirements—challenging the available technologies by definition of Big Data—have spun significant innovation over data management techniques and tools in the last two decades, also leveraging Cloud Computing as an enabler for the new distributed paradigms. For an overall technological analysis of the evolution of Big Data we refer to [68]. Big Data and related concepts are directly implied in I4.0 in general and massively in HC4.0 applications in several ways. Being aware of the great variety of available data sources is of the utmost importance for realizing the actual effectiveness of Big Data applied to HC4.0. The most traditional source of Big Data, that historically led the big-data applications and pushed for the necessary tools, is *Online Social Network data*. Initially aimed at targeted advertising and market analysis, in the context of I4.0 this data is more directly used to tune the value chain, in an automated fashion. From a point of view, whole I4.0 can be seen as an effort to foster such timely feedback from in-the-wild data collection back into the design-production-delivery cycle. For what strictly concerns the health sector, social media are reshaping the nature of health-related interactions, changing the way healthcare practitioners review medical records and share medical information. As access to web resources—in particular to social networking sites and feeds, social-media sources, and on-line discussion forums—provides more and more valuable information, social media and related technologies are dramatically changing medicine practice [69].

Another already present source of Big Data that is increasing its importance in I4.0 is *enterprise data*. Enterprises already produce and manage high volumes of data: besides internal accounting, employee data, internal communications, there are also data custody requirements from regulations. This also applies to healthcare institutions where this kind of data (e.g., administrative, billing, and scheduling information) even if not only and strictly related to the health domain, enrich the list of potential sources, allowing to implement studies that encompass not exclusively biological and medical aspects. In I4.0 this is only expected to ramp up, due to focus on extensive exploitation of the stream of data, enriched with more data sources and with metadata on the process itself. This will add to *external data* (i.e. from outside the enterprise), coming from sold products, customers, and from suppliers/partners, calling for more and more application and evolution of Big Data technologies.

Further increase of data has come from the advancing of technologies. Indeed, stream processing systems monitor people's health status in real time, generating large amounts of structured and unstructured *streamed data* thanks to the fast and significant market penetration of personal devices and the progress in wireless sensors and mobile communication technologies [70]. In addition to this, medical tests, images, and descriptions from clinicians, result in *clinical information* about patients, that is collected through records that may assume several forms and denominations. The most popular ones are [71, 72]: *Electronic Health Records* (EHR); *Electronic Medical Records* (EMR); *Personal Health Records* (PHR). While EHR are intended to report episodes of care *across multiple care delivery organizations*, EMRs are real-time patient health records with access to evidence-based decision support tools, possibly used to aid clinicians in decision-making. PHR are layperson-comprehensible, lifelong tools for managing relevant health information, promoting health maintenance and assisting with chronic disease management and—differently from EHR and EMR—are typically managed by patients.

Moreover, the *scientific literature* still represents an essential source of biomedical knowledge [73] (although structured resources are increasingly available). It requires dedicated text-mining web tools for indexing and cataloging, thus helping users quickly and efficiently search and retrieve relevant publications.

Finally, large amounts of *biological data* in various forms (e.g., genomics, microbiomics, proteomics, metabolomics, epigenomics, transcriptomics. etc.) are today generated and collected at an unprecedented speed and scale [26], since the cost of acquiring and analyzing data is decreasing with technology update. This data can be organized in four different levels [74] (*molecular-level data*, *tissue-level data*, *patient-level data*, and *population data*).

III. HC4.0 Application Scenarios

Market trends as well as scientific literature witness the role of healthcare in being a driver for the main pillars supporting the I4.0 vision. Indeed, considering each pillar, *IoT* is leveraged for remote monitoring in all its facets, thus enabling healthcare implementation in various settings, ranging from long-term elderly care and home surveillance to acute healthcare rehabilitation systems. As these setups produce larger and larger volumes of a wide variety of data by enabling high-velocity capture, discovery, and analysis, new-generation *big-data technologies and architectures* are required to extract value from them [75]. This is further pushing for a shift to *cloud architectures*, needed for securely and reliably handling both processing and storage requirements to analyze these large amounts of data [75].

Figure 3: Main HC4.0 Application Scenarios.

Thanks to IoT, Cloud and Fog, as well as Big Data, researchers and practitioners are allowed to design novel solutions, that are able to efficiently and effectively renew consolidated healthcare practices or even provide novel groundbreaking results to address and mitigate long-lasting healthcare issues. In this section we discuss the main health-related application scenarios enabled by these three ICT pillars and their convergence as stemming out from the scientific literature (with no aim to be exhaustive, see Fig. 3).

A. Monitoring physiological and pathological signals.

The literature shows how the IoT paradigm—supported by the progress achieved in mobile communication technologies as well as in wearables and sensing devices often organized in WSNs and WBANs, together with the availability of on-demand cloud and fog resources and Big-Data technologies—is able to provide a valuable framework to support pervasive monitoring applications. The resulting framework supports the collection of health records, potentially providing the generation of statistical information related to health condition [76, 12, 2, 77, 43], and the delivery of new types of cloud services [78, 79], able to replace or complement existing hospital information systems [80]. This kind of automated approaches guarantee to dramatically lower the risk of introducing errors if compared to methods requiring manual intervention [81]. Systems for patients' remote monitoring consist of three main components [82]: (i) the sensing and data-collection hardware to gather physiological and movement data; (ii) the communication hardware and software to relay data to a remote center; (iii) the data analysis techniques to extract clinically-relevant information from physiological and movement data. According to the type of sensors adopted, applications can be either *in-body* or *on-body* [70]. The adoption of advanced medical and environmental sensors [31, 15]—such as accelerometers and gyroscopes (often integrated in mobile devices), temperature and humidity sensors, as well as ECG, glucose, blood-pressure, and gas, sensors—enables continuously monitor patients' physiological and physical conditions. IoT devices can transmit these data to remote datacenters where data integration can be performed to leverage seemingly infinite storage, scalable processing capability as well as high service availability provided by Cloud Computing [43, 83, 84, 85, 86, 87]. This approach further requires a reliable network connection for remote storage, processing, and retrieval of medical records in the Cloud and imposes many challenges related to network connectivity and traffic [65]. Indeed, among the applicative scenarios driving 5G communication infrastructure evolution, health monitoring is the one listed under *ultra-reliable communications* requirement [27]. Other attempts aiming at mitigating these challenges for improving health-monitoring systems exploit Fog Computing at smart gateways, providing services such as embedded data mining, distributed storage, and notification service at the edge of network to mitigate challenges imposed by the adoption of remote cloud services [51, 66]. Fog computing also plays a major role in augmented-reality latency-sensitive applications (e.g., pervasive brain monitoring applications leveraging EEG-based brain-computer interfaces [88] or cognitive assistance systems [89]). Fog-based architectures are also expected to provide the tools for supporting medical devices to be implanted in human bodies to enhance and restore human functions such as-pacemakers to stimulate the heart muscle, deep brain stimulation system [53].

B. Self-management, wellness monitoring, and prevention.
HC4.0 significantly supports solutions for self-management. Indeed, big-data technologies allow to implement a shift from cure to prevention [19], which is also one of the peculiarities introduced by P4 medicine [24]. Researchers have investigated how to design intelligent services beyond simple functions such as indicating measured data and storing data temporarily, but being able to provide effective feedbacks to individuals. For instance, these solutions can implement algorithms to help prevent diseases by identifying modifiable risk factors and designing interventions for health behavior change [90]. Management of chronic diseases is another of the most important examples of these self-management for health. For instance, considering the management and prevention of diabetes and obesity, these systems are able to provide suggestions for educating to and empowering good nutritional habits [91, 92] and plan fitness programs [38, 14]).

C. Medication intake monitoring and smart pharmaceuticals.
Medication noncompliance is common in elderly and chronically ill subjects and is exacerbated in case of cognitive disabilities. Monitoring medication intake addresses related issues. In addition, these systems are a valuable tool for clinicians in disease management as they provide a quantitative way of assessing treatment efficacy [82]. Early prototypes designed for the elderly leveraged combined use of sensor networks and RFID [93]. According to the extreme relevance of timing of drug delivery in drug treatments for achieving the optimal effectiveness and minimizing adverse effects, several mobile apps are today available that have features such as reminder scheduling, prescription reminder and medication intake tracking [94]. Advanced solutions (e.g., consisting of wearable or ingestible sensors, as well as integrated IoT connectivity and intelligence) are also being presented [95]. In this context, *smart pharmaceuticals* are defined as electronic packages, delivery systems, or pills that provide intelligent added value [96] (e.g., through a wireless connection to an internet-enabled device or direct internet communication that allows communication to a remote system that can compile, store, and analyze the data). Future smart pharmaceuticals are expected to collect a range of micro- and macro-level metadata able to offer new insights into disease, aid service design, and facilitate personalized healthcare.

D. Personalized healthcare.
Personalized healthcare is intended to be *user-centric* i.e. it aims at taking patient-specific decisions (rather than stratifying patients into typical treatment groups) [14, 44, 97, 2]. Gathering data from multiple sources (e.g., from both patients and the environment) is crucial, as related data analysis facilitates health and social care decision making and delivery. Typical sources can be wearable (or even implantable micro- and nano-technologies) with sensors or therapy delivery devices, such as fall detectors, implantable insulin pumps, defibrillator vests, etc. These properties (namely, *user-centrality* and integration of data from *multiple heterogeneous sources*, including wearable devices, to offer highly personalized services) are typical of the I4.0 vision. They strongly characterize HC4.0 and are further emphasized when considered under the *P4 Medicine* paradigm [24, 25, 98, 99, 100], that heavily relies on the genetic information of each individual. Indeed, comprehensively understanding the biology of each individual (*personalized omics*) allows to impact on predisposition, screening, diagnosis, prognosis, pharmacogenomics, and surveillance [26]. Accordingly, big-data analytics is crucial for implementing personalized healthcare, both at individual and population level [100, 97, 101].

E. Cloud-based Health Information Systems.
In a number of cases, cloud-based architectures have been largely adopted to strengthen and simplify the design, the development, and the deployment of information systems, for collecting, processing, and sharing clinical records [102, 103, 104, 105, 106, 107, 108, 109, 110], hospital administrative information [111], or medical images [112, 113, 5, 114]. These architectures, help enhance the data collection process (e.g., the involved entities are often provided with mobile user interfaces to cloud services for gathering and managing healthcare information [114]). Furthermore, information sharing across different medical structures [112, 105] or between hospitals and patients [105, 103] is also benefited, as in

several cases these systems also aim at integrating data in several different formats [106, 63, 111] Although concerns about system performance are taken in consideration only in few cases [106]. the design of these systems focused often on security and privacy aspects, that are both considered as critical.

F. Telepathology, telemedicine, and disease monitoring.

First noticeable attempts for practical telepathology, i.e. the remote acquisition, transmission, and inspection of pathology specimens, date back to the 1980s, when the integration of robotic microscopy, video imaging, databases, and then-seminal availability of broadband telecommunications was envisioned as the infrastructure for supporting telepathology services [115]. This promise has proven true, as of today many contributions are available, showing how ICTs support a plethora of different applications related to telemedicine, telepathology, and disease monitoring [116, 31]. Available studies can be divided in two classes: i) generic frameworks, applicable to the vast majority of use cases [117]; ii) works focused on specific diseases, such as cancer detection, cardiovascular diseases [118], diabetes [119], Parkinson [120], and Alzheimer [121]. These monitoring systems can be in turn adopted both to feed large-scale studies, and to inform treatments tailored according to the results of the specific individual (as in the *P4 Medicine* approach).

In the future, also surgery is expected to become more transparent. Indeed, video cameras are often integrated in operating-room lights for open surgery. Accordingly, the surgical procedure becomes potentially visible to an unlimited number of spectators. These tools enable *teleconsultation* which allows to avoid the physical presence of the consultant. If an active camera holder is used during a surgery, *telepresence* may take place, in case the remote consultant can move the camera. *Telesurgery* represents the final evolution of this application scenario, with the surgeon and his/her cockpit being physically separated from the operating room [96].

Since best-effort Internet connections are not enough to support several classes of applications (e.g., when the goal is recreating the effect of a microscope locally handled), the availability of constrained virtual paths to Fog services at the edge can help fill this gap. For instance, it can enable remote federated sites to collaborate on non-trivial diagnoses e.g., providing tools for offloading complex image processing and data mining tasks without suffering higher delays of a Cloud access.

G. Assisted living.

A side-effect of better nutrition and overall better healthcare is the increasing aging of world population, that therefore is likely to become the more and more an issue in the future. As a way to deal with the growth of costs associated with elderly and individuals with chronic conditions [39], *aging in place* has been proposed, i.e. to avoid unnecessary hospitalization by allowing patients to remain in the home environment, in so-called *enhanced living environments* (ELEs). Several ICT technologies are involved in this kind of solution, as described in the following. Remote monitoring of patients is required for safety and for facilitating the implementation of clinical interventions [82], while telepresence and video-conferencing robotic solutions (e.g., equipped with display and webcam and remotely controlled over the Internet) have been proposed [122] to better connect older people with other persons (e.g. distant relatives, or physicians) without moving or traveling, and without requiring to learn new technologies. As the overall health condition of elderly and people with disabilities can be estimated from their heart beat rate, blood pressure, and accelerometer data, wearable sensors and thus WBAN technologies are of utmost importance for assisted-living facilities. Specially in home environments, WBANs can be integrated with ambient sensors to create an *ambient-assisted living, AAL* [95], where the parameters of the living environment can be sensed and controlled, and body data can be delivered to a central station. In order to make sense of the huge amount of monitoring data, and to efficiently scale with the number of patients being ambient-assisted, artificial intelligence methodologies can be adopted for *ambient-intelligence systems* in the healthcare domain, providing automated learning, reasoning, and planning capabilities [123]. These technologies would allow to automatically alert a healthcare center for observation and emergency assistance, in case deviations from the normal activities and parameters are detected [123], or for less urgent cases would allow to propose medical or life-style engagements [124]. As with other applications, Cloud and Fog technologies can provide the on-demand infrastructure (with desired communication and processing capabilities) necessary to collect patients' data in real time and process it, supporting pervasive healthcare and AAL [125, 62, 126].

H. Rehabilitation.

In line with assisted living, *home-based rehabilitation* is expected to bring significant cost savings for the healthcare systems and better quality of life for the patients. Likewise, WBAN technologies are the main tool allowing detection and tracking of human movement associated with rehabilitation practice. Different from generic assisted living solutions, home-based rehabilitation is characterized by a number of specific constraints and requirements, and associated solutions [127, 116], involving multi-sensor data fusion, real-time feedback for patients, and virtual-reality integration. A key feature provided by WBANs in home-based rehabilitation is related to *biofeedback*: the measurement of physiological activity and other parameters, fed back to the users themselves. This practice effectively enables the patient to control and modify their physiological activities, with the final goal of improving their health and performance [116, 128, 129, 130].

IV. Discussion

The new technological paradigms converging in the Industry 4.0 are generating a profound change in mindset and approach to traditional applications. This phenomenon is in development also for the sector of healthcare, that already started a progressive transition towards e-health, expected to further expand and accelerate in the HC4.0 scenario. The mindset change will imply the understanding of new possibilities and opportunities as well as new challenges and risks: in this section we discuss both aspects (summarized in Tab. II), to foster a conscious and effective integration of new methods, technologies and tools in the healthcare processes.

Table II: Main benefits and challenges from the adoption of I4.0 pillars in healthcare.

	Benefits	Challenges
IoT	• enhanced electromedical devices (*closed-loop design, predictive maintenance, new service lines*) [131] • interoperability, evolvability thanks to *open communication standards* [132]	• energy constraints [133] • security [134, 135, 136, 81, 137, 138]. • scalability [81, 139, 133, 31, 135]
Cloud/Fog Computing	• *infrastructure for high-level functions* (data analysis, information systems) [102, 103, 104, 106, 107, 110, 5, 111] • *paradigmatic model* for offering of services to patients or to healthcare operators themselves [47]	• performance monitoring • opacity of the infrastructure [109] • data privacy [18, 52, 109] • infrastructure availability [18, 16]
Big Data	• new insights and *actionable information* from new data sources [140] • natural transformation of *descriptive* research into *predictive* and *prescriptive* one [141]	• extreme heterogeneity [142] • opacity of analytics [143, 144]

A. Benefits

Several positive aspects of the IoT apply to healthcare almost fully when considering electromedical devices or pharmaceutics industry. With reference to these, IIoT carries a number of benefits [131, 145, 146], the most relevant summarized in the following. **Closed-loop design**—Feedback on product usability and effectiveness from physicians, health operators, and patients themselves can be constantly put back into the design phase: analyzing real-world usage data, designers better understand how products are being used and can design improved versions. **Predictive maintenance**—thanks to the ability to continuously gather data, IoT enables fault prediction and thus maintenance before failures occur, allowing for timely servicing or substitution or avoiding machine downtime altogether. The impact of such possibility on economy and management of life-critical services can be hardly overstated. **New service lines**—manufacturers can offer better or more convenient remote monitoring and maintenance services, through devices that can be continuously improved or fixed.

Electro-medical devices communication systems have requirements centered around robustness and reliability, and also often tightly bounded latency and jitter. In addition to these, the robustness to mutual radio interference is required to allow the coexistence of multiple wireless networks, with different radio technologies, in small volumes (the close surroundings of a human body). The ongoing **development and wide adoption of open standards** for protocols designed with these constraints (IEEE 802.15.6 and IEEE 802.15.4) [132]) means that a variety of non-mutually exclusive solutions will be available, also improving interoperability between devices and components from different vendors (with consequent reduction of costs, and improved evolvability of the whole system). Along these lines, in the last decades, in the IT world the ubiquity and interoperability of the TCP/IP communication stack has already provided real-world testing and wide adoption of wireless local area networks (Wi-Fi) and their interconnection to the Internet, recently expanding from the original Small-Office-Home-Office scenario also in the much more demanding industrial scenarios [147]. The technologies are thus ripe to allow the HC4.0 to extensively benefit from them, merging (Wireless) Body Area Networks, Personal Area Networks, (Wireless) Local Area Networks, Internet technologies, but also the Internet itself, as a global communication infrastructure.

The overall picture emerging from the state-of-art is that Cloud Computing is a fundamental enabler for HC4.0 first of all as an extremely powerful and cost-effective infrastructure for high-level functions (data analysis, high-end information systems), but also as a paradigmatic model. The first aspect is the charaterizing function of Cloud technologies, whose main properties have been introduced in Section II. Regarding the second aspect, Cloud Computing inspires (and provides the means to) **Healthcare-as-a-Service mindset**, both for the offering of healthcare services to patients, and for the usage of analysis, diagnostic, communication services for healthcare operators. In offering services to patients, healthcare operators can consider providing remote front-office, remote consulting, etc. knowing that such services have high impact on time, transportation, and comfort for patients and can cover much broader population at a fraction of the cost compared with in-person activities, thus will result in better quality of life for patients (and some categories of operators) and competitive advantage for operators in the private sector. Similarly, healthcare operators can benefit from best-of-breed, physical-location-independent, fully outsourced, and cost-effective services that are offered through Internet—backed by Cloud technologies—e.g. as Software-as-a-Service. Fog computing in turn can provide the technical means to enjoy the same benefits above mentioned while using mobile terminals, that are ubiquitous and personal, thus already familiar to large part of population. Regarding the pharmaceutical industry, Cloud technologies are the essential enablers for achieving (logical) decentralization of manufacturing execution and planning systems [148], and for allowing seamless introduction of human intellectual work where and when needed (e.g., crowdsourcing difficult tasks [149]). For all these reasons the future of HC4.0 will be even more tightly bound to the research on Cloud Computing and its evolution.

Big Data techniques are fulfilling the promise of extracting value (actionable information) from amounts of data previously unthinkable or unmanageable. The operators in healthcare sector can now explore their processes looking for new possibilities of continuous and massive data collection, knowing that Big Data techniques have the potential to extract new meaning and useful information from it. Adopting a big-data approach, the medical researcher can naturally transform *descriptive* research questions (*what happened?*) into *predictive* ones (*what could happen?*), with the aim to reach the *prescriptive* ones (*what to do, to get one specific achievable outcome?*) [141]. By discovering new data sources, or applying the derived data-driven results, the stakeholder in healthcare sector can effectively use big-data analytics to reduce concerns and uncertainty, and ultimately causing the improvement of the healthcare system [140] in one of its many aspects. Indeed, big-data analytics can contribute to evidence-based medicine, genomic analysis, as well as to patient-profile analyses, or pre-adjudication fraud analysis. More in general, big data technologies will provide insights to reduce inefficiency, be it in clinical operations, public health, or research and development [150, 151].

B. Challenges

In general terms, IoT is in its infancy in the healthcare field [14]. Considering that IoT consists of interconnected smart objects, most of the issues regard the design of either smart-objects and communication technologies. **Energy** is a major technical challenge. In fact, research is needed on energy harvesting, energy conservation, energy and usage, to design and develop zero-entropy systems systems harvesting energy from the environment and not wasting any under operation [133]. **Scalability** is another important challenge to be addressed, that is exacerbated by the specific domain. Indeed, interconnected objects will outnumber by several orders of magnitude those composing classical Internet (IoT is expected to be composed of up to trillions devices) and healthcare services are generally characterized by high demand. Therefore, because of the potentially drastic escalation of the connected devices, architecture scalability is among main concerns [81, 139]. For instance, performance and manageability would benefit from organization in hierarchical subdomains [133]. Specific design issues are dictated by the deployment and adoption of BANs [31, 135]. Moreover, further research is required to develop and design appropriate IoT **security** solutions, e.g., primitives resilient to run-time attacks as well as scalable security protocols. As for today, IoT systems are not sufficiently enhanced to fulfill the desired functional requirements and bear security and privacy risks [134], specially when also addressing scalability requirements [135]. Existing security solutions are inappropriate since they do not scale to large networks of heterogeneous devices and cyberphysical systems with constrained resources and real-time requirements. Moreover, as sensors that monitor health signals continuously generates enormous data (often feeding critical applications), secure and effective architectures are needed for organizations to process the big data in integrated industry 4.0 [152]. The scientific literature witnesses how protecting IoT requires a holistic cybersecurity framework covering all abstraction layers of heterogeneous systems and across platform boundaries [134]. Additional security implications are generated by connected healthcare devices (e.g., wearables) that can be at risk to hacking and hence may need a secure uniqueness management and authentication to be implemented [136, 81, 137]. Therefore, due to the resource limited devices usually adopted, it is an essential requirement to design lightweight algorithms in the secure data management system [138]. One of the main issues with Cloud is more essential to its nature: it provides its as-a-service facilities with appealing prices by masking the real infrastructure, sparing the cloud customer to manage the details of operations related to the cloud resources, and offering economies-of-scale grade prices [152]. While these are exactly the desired properties of Cloud Computing, the **opacity of infrastructure** can become a limit when performance is required. Indeed, computing performance [153], efficiency of communication protocols [125], network performance (e.g., because of poor bandwidth and unpredictable latencies when transferring high volumes of traffic) [83, 18, 84, 154, 110, 155], still represent barriers. Moreover, although cloud technologies are known to be scalable, works in the literature report scalability of the implemented solutions to be a common concern [85, 156, 157]. We refer to [158] for an analysis of issues and techniques in Cloud status and **performance monitoring**. Recently, according to the increasing adoption of systems implemented through public clouds, research has also focused on the performance of public-cloud networks [159, 160]. According to the above considerations, when dealing with data intensive applications, **co-design approaches** involving different stakeholders (particularly those in network/performance engineering roles) have to be taken into account to manage and troubleshoot service performance [161].

Introducing the Fog paradigm brings additional open issues to be properly addressed to make the Fog a reality in the healthcare context. The Fog exacerbates scalability issues as it potentially deals with billions of small devices to be configured (e.g., due to the possible integration with BANs). and requires scalable and decentralized management mechanisms that need to be properly tested at this unprecedented scale [52], Computing nodes and applications running on top of the Fog also need to be properly configured. In addition to this, safety, reliability, availability, flexibility, maintainability, and power efficiency are commonly considered issues [162].

More in general, since Cloud and Fog solutions allow applications to process users data in third-party's hardware and software, their adoption introduces strong concerns about **data privacy** [52]. These issues often derive from the concern of loosing control over data [18] due to the limited confidence in the provider in charge to store very sensitive information in its infrastructure [109]. Some proposals to solve these issues are being proposed recently, e.g. [163] introduces an *Identity Management* architecture enabling patient-controlled partial disclosure of EHR to selected recipients. These solutions have yet to see validation, standardization, or wide adoption, and come to additional complexity costs, still to be assessed. Therefore this remains an open and hot research field.

However, provided solutions increasingly leverage external services as replacement of in-house solutions, as the former are often equipped with advanced security settings (e.g., they adopt proper encryption algorithms, such those used by the financial sector [164]). Moreover, these services offer increased **availability**, helping to provide uninterrupted delivery with minimum downtimes [16]. In the case of critical applications, availability remains a concern, specially if access technologies (prone to service outages) are involved. High reliability is indeed one of the goal of 5G communications technologies, but at the time of writing only experimental deployments have been performed, so their pace of adoption (and the geographic and population extent of their coverage) are still to be known. It is worth noting that a temporally or spatially uneven deployment of 5G technologies would arguably create or worsen unprecedented levels of *digital divide*, instead of relieving it. To further improve availability for critical services, multi-cloud solutions have been also proposed [165]. Depending on the kind of cloud service that is leveraged (SaaS, PaaS, or IaaS), the promises of the Cloud paradigm can be achieved by means of intelligent dynamic allocation of physical and virtual resources. This process is computationally high demanding and will require cloud resources itself, moreover its complexity is expected to dramatically grow in the context of I4.0: this is currently an open issue, requiring its own part of future research [166].

Because of its characteristics, the huge amount of healthcare-related data satisfies the requirements (in terms of volume, velocity, and variety) to be considered as Big Data [150]. Among its peculiarities, a significant challenge for HC4.0 (highlighted and addressed within the Big Data paradigm) is **heterogeneity of sources, formats, attributes of data** (an extreme example of big-data *Variety*): Jirkovsky et al. [142] focused on semantic heterogeneity and propose a framework to foster interoperability. Moreover, due to constant real-time monitoring—that is of the utmost importance in many medical situations—*velocity* of mounting data has increased with respect to traditional static healthcare data. Indeed, its volume is growing exponentially, requiring proper solutions to store larger and larger amounts of information. All these aspects make healthcare data both interesting and challenging. Finally, considering that big-data analytics and outcomes have to be error-free and credible, big-data techniques, due to novel usage of machine-learning algorithms on unparalleled and unknown-before amounts of data, present an **opacity** issue, that is most significant when dealing with health, life-related decision, and high-impact and social relevant matters, such is the case with HC4.0 [143, 144]. The issue of lack of transparency in Big Data has been raised so far mainly regarding the fields of AI and Robotics, discussing its relationship with regulation and innovation [167] without reaching a solution.

C. Patients and Professionals

To take into account also non-ICT actors directly involved by Healthcare 4.0, we here discuss also the viewpoint of healthcare professionals and patients, referring to surveys that investigate on the acceptance of technologies at the basis of Healthcare 4.0, to extrapolate sensible expectations regarding their evolution.

In an online survey in collaboration with the Northern Norway Regional Health Authority and the Norwegian Directorate of eHealth, the authors of [168] investigated hospital **health professionals**' experiences for the case of patients accessing their own EHRs, also looking for differences in experiences and attitudes according to hospitals, doctors and nurses, and between psychiatry and somatic care. The results revealed positive experiences, including patients highlighting mistakes and omissions in their own EHR, and also being better informed about all the aspects of their healthcare. Minor differences in experiences and attitudes were found based on practices at the different hospitals, and between doctors and nurses, while major differences in experience and attitude were found between psychiatric and somatic care. Health professionals working in psychiatry questioned the suitability of the service for the sickest and most vulnerable patients, suggesting that adaptations, or training might be necessary for EHR access by patients in psychiatry field. EHR represents a necessary component of an evolution from e-health to Healthcare 4.0, especially in the scenario of self-management, therefore we can project to Healthcare 4.0 both the expected positive outcomes, further emphasized, and also the caveats and skepticism raised by healthcare professionals in specific fields (namely, psychiatry).

Regarding the **expectations on patients experience**, both the analyzed scenarios B and C (Self-management, wellness monitoring, and prevention; Medication intake monitoring and smart pharmaceuticals) are involved in the study [169], where a smartphone app was used to gather evidence-based information on effectiveness of Adjuvant Endocrine Therapy (prescribed for reducing reoccurrence risk of breast cancer), together with an electronic side-effects diary, a peer support forum, and a repeat prescription reminder. The objective was to counter the low adherence to the therapy over the prescription years, that results in a two to three-fold increased risk of mortality. The qualitative survey explored the acceptability, the perceived usefulness of the services provided through the app, and its usability. The findings showed that the patients almost unanimously appreciated the app and valued the services provided through it, supporting the hope that higher adherence to the therapy and therefore lowered risks will be attained in the future years. Single cases did not value the app more than the information provided by health professionals in person. Moreover the disadvantage has been highlighted regarding lack of access for those with low incomes, rural communities, older people, who would experience higher difficulties for these e-health platforms. Similar results, both positive and with warnings and caveats, emerge from the literature [170].

On the one hand, these aspects can be extrapolated to the Healthcare 4.0: a continuous, simpler, and bidirectional exchange of information among patients and a more handy and accurate monitoring of both health conditions and medicine intake well represent the objective of Healthcare 4.0 new technologies. Likely, these new services will further deepen the difference of experience and service between medium-high income, young, well-educated patients and low-income, or otherwise disadvantaged ones: special care should be taken in preferring technologies that have the broadest accessibility. On the other hand, Healthcare 4.0 is already pursuing the goal of extending the population served with high-quality healthcare, specifically in scenarios D, F, G (Personalized healthcare; Telepathology, telemedicine, and disease monitoring; Assisted living) whose traditional versions are heavily limited by economics, and thus available to a restricted affluent or privileged population. Further challenges regard the acceptance and usage of technology by users for their own healthcare: we refer to [171] for a meta-analysis of studies on this specific aspect.

V. Lessons Learned

The evolution of ICTs is deeply transforming all human activities, heavily impacting also the healthcare sector. From our analysis we have derived the following main lessons. First, both the technological possibilities and above all the innovating mindset brought forth by HC4.0 are reshaping the vision of the future of healthcare, into the *ubiquitous* and *continuous* availability of *personalized* medical services. Among the technical innovations behind this vision, specially wearable devices, the IoT, and its health-related specializations (e.g., Internet of Medical/Health Things) are the most evident pillars sustaining HC4.0, being easily recognized as the newly improved, more powerful, and less constrained versions of medical sensors and equipment. Wireless Body Area Networks, integrating also nanoscale sensors and devices, are at the forefront of such technologies. The impact on wellbeing and on the overall quality of life—for both healthy people and diseased patients—is easier to envision, as good habits and timely treatments are promoted while hospitalization and healthcare costs are reduced. Another clearly recognizable innovation fueling HC4.0 regards the Big Data analysis tools and platforms—including Artificial Intelligence techniques—that in turn extract the knowledge hidden in massive amounts of data fast flowing from the ubiquitous wearable sensors: based on future populations studies of unprecedented size and richness, previously undetectable patterns and correlations will be revealed and exploited, further advancing prevention and cure possibilities.

Other technologies, such as Cloud/Fog computing—and the rising 5G telecommunication infrastructure integrating it with IoT—are less immediately recognized as pillars for HC4.0 as they work "behind the scenes". However, they are (or will be) essential to the novel applications for providing the basis for the *ubiquity* of the medical services and the required *performance* at an affordable cost. These less evident technologies contribute also to the shared drawbacks, limitations, and issues of future health-related applications: (i) security of devices, communications and processes; (ii) privacy and ethical issues related with extensive monitoring, selectiveness, and massive automation of health-related processes; (iii) unprecedented complexity of systems backing the new applications, limiting or altogether impairing their full understanding (and thus, control); (iv) the fast pace of technical innovation, hard to catch-up with regulation and civic vigilance; and (v) the intrinsic multidisciplinary nature of HC4.0, including many technical fields and deeply involving non-technical areas as well.

Some of the issues are well-known and cross multiple research fields: security and privacy are the most prominent and well studied. Nonetheless, the integration of different technologies and above all their application to novel scenarios call for an ever-renewal of the study of the issues and research of new solutions. This is further worsened by the implicit trade-off and the inter-relation between some solutions and other issues: this is the case of the enhancement of security, often causing also an increase of complexity, in turn challenging transparency and understanding of the system, that impairs vigilance and regulation, that potentially can hamper fast innovation. All these issues must be accounted for, and at least a basic knowledge of the technological pillars that are affected by them, with their characteristics, inter-relations, potential, and limitations, is necessary to a conscious, controlled, and full progress of HC4.0.

VI. Conclusion

This work is intended as a reference aimed at helping researchers and practitioners in ICTs in applying their expertise to address the needs of the healthcare sector, and those in the field of healthcare information systems and automation to effectively and profitably face the new concepts and approaches coming from the IT field and constituting the envisioned HC4.0 evolution.

We have introduced and discussed in depth in Section II the main groups of technologies from the so-called *Fourth Industrial Revolution*, namely the Internet of Things, Cloud and Fog Computing, and Big Data Analytics, focusing on their application in the Healthcare sector. From such analysis of literature we have surfaced how this specific sector, already moving towards an ICT-backed *e-health*, will experience further radical transformation in the new context of *HC4.0*, in which ICTs not only offer **improvements for traditional processes and systems** like Cloud-based Health Information Systems, Advanced Monitoring of physiological and pathological signals, medication intake, and activities, but inspire and make possible **new unforeseen approaches, processes, and applications** such as Enhanced Living Environments, Home-based Rehabilitation, Personalized Healthcare (Section III). We have discussed a number of strictly **technical benefits** (closed-loop design, predictive maintenance, advanced service lines, development of open standards) at the basis of the aforementioned technologies, together with the related **technical challenges** (opacity of the infrastructure, need for monitoring, heterogeneity of formats and standards), detailed in Section IV. Finally, Section V draws the main lessons learned that cross the pillars and involve non-strictly-technical aspects.

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