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Insight Report

Health and Healthcare in the Fourth Industrial Revolution

Global Future Council on the Future of Health and Healthcare 2016-2018

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World Economic Forum
91-93 route de la Capite
CH-1223 Cologny/Geneva
Switzerland
Tel.: +41 (0)22 869 1212
Fax: +41 (0)22 786 2744
Email: contact@weforum.org
www.weforum.org

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Executive Summary

The World Economic Forum Global Future Council (GFC) on the Future of Health and Healthcare comprises expert stakeholders representing the public and private healthcare sectors. For the 2016-2018 mandate, members of the GFC worked together to provide insights on how the evolution of global health and healthcare will affect us all in the decades to come, including through the implementation of the Fourth Industrial Revolution.

It is now well recognized that the misalignment of all stakeholders resides at the core of health sector underperformance. This is largely due to narrow competing objectives (silos versus different incentives), power asymmetries (North versus South, advanced versus emerging economies) and cooperation failures among other things. However, these challenges will have to be addressed collectively as health- and healthcare-related issues have become some of the most prominent preoccupations for people across the globe and generations.

First and foremost is the pressing issue of seeking sustainability: from our ageing demographics (by 2050, one fifth of the global population will be over 60 and two thirds of babies born today could live to 100) to the increasing burden of non-communicable chronic diseases (NCDs), which already represent 75% of healthcare expenses, while the rising cost of healthcare will contribute to an overall direct and indirect loss of $47 trillion for the world's gross domestic product by 2030.

Second, the acceleration of science and discovery with, for example, the cost of genome sequencing falling below $1,000, and over 100,000 new drugs in the pipeline, some of which have already had a profound impact in developing cures, particularly in cancer, but are increasingly associated with unaffordable costs. For example, recent approved cell therapy costs well over $1 million for one treatment for a single patient.

Third, the progress in technology spanning the digitalization of health and healthcare to social media, internet of things (IoT), wearables, sensors, big data, artificial intelligence (AI), augmented reality (AR), nanotechnology, robotics and 3D printing, which together will radically transform society, increasing interconnectivity and breaking the structures of healthcare systems.

The 2016-2018 Global Future Council on the Future of Health and Healthcare examined how these advances in discovery and clinical sciences, data science and technology and their convergence are paving the way for exciting new developments. Specific examples of breakthroughs include genetic engineering – especially genome editing – regenerative biology and medicine, tissue engineering, cancer genomics and immunotherapy, precision medicine, microbiome, optical imaging, optogenetics and brain machine interface technology. In addition, the surge of data science with big data analytics, digital technologies and AI will have a transformative impact on health and medicine. If the aforementioned achieve their potential, we will see transformative effects across all aspects of health and healthcare.

Indeed, certain advances will go beyond transforming disease treatment and prevention; they will effectively offer a cure for some diseases. For example, gene-editing technologies have the potential to cure genetic diseases, such as sickle cell disease and cystic fibrosis. Germline editing has the potential to cure diseases with permanent intergenerational changes, while somatic genome editing can treat, control and possibly cure acquired diseases.

Advances in precision medicine can guide healthcare decisions towards the most effective treatment for a given patient or subset of patients. Furthermore, precision medicine holds great promise for prevention and public health, particularly by identifying predisposed or high-risk patients for specific conditions and diseases that could be readily prevented with early detection, appropriate screening or through lifestyles changes.

Though healthcare is somewhat behind when it comes to big data compared with other sectors or industries, it certainly is catching up with massive information generated. Healthcare data captured in real-time can generate new knowledge and evidence to better understand patterns of health and disease. The access to real-world evidence will play a critical role in the development of a system in which, "science, informatics, incentives and culture are aligned for continuous improvement and innovation, with best practices seamlessly embedded in the delivery process and new knowledge captured as an integral by-product of the delivery experience[1]".

The integration of big data, analytics, new technology and connectivity inside and outside clinical encounters, coupled with payer activity and cost, pharmaceutical and medical products R&D data, and patient behaviour, will help us better predict the outcome of diseases as well as drivers of health, including social determinants which are often underappreciated.

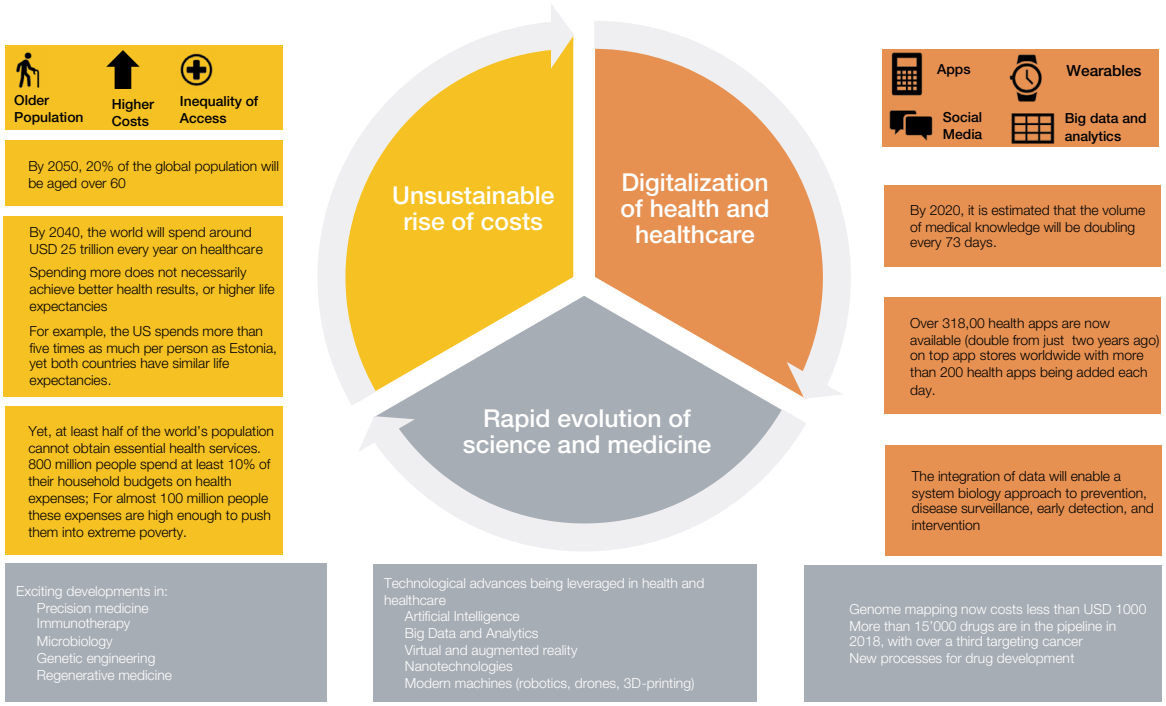
In the future, two fundamental shifts will reshape the healthcare industry. First, healthcare will be delivered as *a seamless continuum of care*, away from the *clinic-centred point of care model* and with a greater focus on prevention and early intervention. Second, health and healthcare delivery will focus on each person within their own ecosystem, with a greater impact from people or patients themselves, often referred to as *the consumerization of healthcare*.

Telehealth technologies will enable patients to send personal information to providers who can remotely diagnose health problems; IoT and other technologies will enable real-time monitoring; and technologies such as apps and wearables will help promote healthy behaviours and enable sustained behaviour modification. Finally, AI is likely to transform all areas of health and medicine towards clinical decision-making.

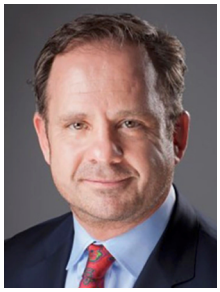
Across systems, the integration of these approaches will serve as a foundation for value-based care approaches and value-based payment models, focusing on improving individual outcome while optimizing the cost of care per patient. Improving care outcome through rationalization at the point of care will help reduce redundancies and waste, estimated at up to a third of the current total spend for healthcare. This will improve outcome and efficiency of healthcare delivery, while controlling costs and keeping innovation at the centre of future health and healthcare enterprise.

Despite the mounting challenges facing health and healthcare delivery, our council was able to provide promising insights and perspectives, thanks to all its members' collective expertise. The combined advances in discovery and clinical sciences, data science and technology and their convergence through the Fourth Industrial Revolution, are paving the way for unprecedented changes, which will profoundly transform health and healthcare to become much more connected, efficient, preemptive, precise, democratized and affordable. Not only will this improve the health of individuals, it will also reduce imbalances across geographies while boosting economies and spurring employment, a key factor in the wellness and health of society.

Figure 0: What is driving innovations in health and healthcare?



Foreword



Andre Goy, Council Co-Chair; Chairman and Executive Director; Chief of Lymphoma, John Theurer Cancer Center, Hackensack University Medical Center

Sania Nishtar, Council Co-Chair; Founder and President, Heartfile

Victor J. Dzau, Council Member and Co-Lead Author; President, US National Academy of Medicine

Society is in the midst of transformative changes. Klaus Schwab, in his book, *The Fourth Industrial Revolution*, notes that we are at the beginning of a revolution that is fundamentally changing the way we live, work and relate to one another. The scope of the Fourth Industrial Revolution is broad and is characterized by a fusion of technologies across physical, digital and biological domains.

It is disrupting almost every sector and industry in every country and creating massive change in a non-linear way at unprecedented speed.

Indeed, the Fourth Industrial Revolution is transforming health and medicine due to the lightning-speed advances in genomics, genetic engineering, synthetic biology, nanotechnology, data science, AI, robotics, to name just a few. These scientific and technological advances promise to yield breakthrough diagnosis and therapies including precision medicine and medical cures. Medical and technological breakthroughs and advances will transform health and healthcare to become much more connected, precise and democratized, with significantly improved human outcomes.

At the same time, innovations and technologies inevitably carry risks and raise important questions. For instance, rising healthcare spending and the unaffordability of treatments are already a global challenge, and there are concerns that expensive new treatments and technologies will only exacerbate these trends. Technology may deepen healthcare inequalities by perpetuating existing biases in research results based on data that might lack diversity of gender, race and age. Health professions will need to acquire new knowledge and skills to utilize new technologies and adapt to changing modes of care delivery.

To comprehend the scope of scientific and technological breakthroughs and their potential impact, the 2016-2018 Global Future Council on the Future of Health and Healthcare[2] prepared this report to serve as a key resource in understanding the effect of the Fourth Industrial revolution on health and medicine. Through a series of case studies, it seeks to characterize how this revolution in health and healthcare will affect us in the coming decades and to discuss the societal implications and governance of key emerging technologies related to health and healthcare.

Our hope is to promote understanding of these groundbreaking technologies, identify the challenges they will bring, raise awareness and stimulate dialogue, and drive collaboration between policy-makers and innovators.

We, the Co-Chairs of the 2016-2018 council, and a co-lead author, were privileged to work with the members of the council who have provided important insights and dedicated significant time to completing this report. Without the contributions of all these individuals, this report would not have been possible.

Introduction

By 2050, the world will be home to 10 billion people, and two in five of these people will be aged 60 or over, including 434 million over 80 years old.[3] This combination of population growth and demographic changes will seriously accelerate the challenges we face for the delivery of health and healthcare, with global healthcare spend projected to reach 13% of GDP in OECD countries by 2050.[4]

Over the past century, tremendous strides have been made across various facets of health and healthcare. From the promotion of antiseptic surgery and use of antibiotics in the early 1900s to genome editing in the 2000s, new science and innovations have driven substantial improvement in care delivery and outcomes. However, the rapid population and societal transformations of the next few decades will require the deployment of better tools and technologies that will enable us to lead longer, healthier and more productive lives while controlling non-sustainable cost and achieving better access to care for populations across the world.

Within this context, this report is an undertaking by the 2016-2018 Global Future Council (GFC) for Health and Healthcare, an interdisciplinary knowledge network of thought leaders from academia, government, business and civil society, hosted and convened by the World Economic Forum. The network is promoting innovative thinking and thought leadership in the field. It aims to provide insights on how the revolution of health and healthcare will affect us all in the decades to come as part of and beyond the Fourth Industrial Revolution, and to develop new insights and perspectives on the impact and governance of key emerging technologies related to health and healthcare.

Members of the council selected four technology-focused key themes to be featured in the report: medical breakthroughs in biotechnology; enhancing human health for improved wellness; analytics and computing for improved diagnostics, payments and information sharing; and modern machines and healthcare.

This taxonomy built further on the categorization outlined in the World Economic Forum's seminal report, *Shaping the Fourth Industrial Revolution*,[5] to some extent but was largely driven by the collective knowledge and expertise of the GFC members. For each technology and innovation included, an integrative literature review[6] was performed to define key concepts and synthesize research and policy discussions. Four inclusion criteria were used to select case studies featured in the report. Cases had to be verifiable, relevant to the four pre-agreed key themes, non-commercial in nature, reported within the past decade, with demonstrated positive benefits for health and/or healthcare.

This report is by no means exhaustive. Our hope is to contribute to promoting discourse and understanding of these groundbreaking technologies, as well as the challenges they will bring, to raise awareness and stimulate conversation, driving collaboration between policy-makers and innovators.

Medical Breakthroughs in Biotechnology

The acceleration of progress in biotechnology is redefining what is achievable, to the benefit of patients. Biotechnology is the common term used to describe the exploitation of biological processes, organisms, cells or cellular components to develop new technologies.[7] From a health and healthcare perspective, this significantly improves our ability to leverage this knowledge to provide innovative and transformative therapies.

Genetic Engineering

Genetic engineering refers to the precise manipulation of the genetic material of an individual using biotechnology. This includes options like gene therapy (the process of providing a patient with a functional copy of a detective gene causing a genetic disease), gene editing (making precise additions, deletions and/or alterations to the complete set of genetic material in an organism), or exon skipping, which consists of skipping the genetic mutation in the gene during transcription (therefore removing the negative effect or consequence of a given mutation).

Over 10,000 human diseases are caused by genetic mutations.[8] While a few can be treated by providing a synthetic version of the missing protein to the body, most do not yet have a cure because they require the missing or defective gene to be produced on-site. For these patients, care had been mostly limited to addressing symptoms and help support their chronic condition.

Table 1: Successes and promises in genetic engineering

Haemoglobinopathies
Haemoglobin, the oxygen-carrying component of the red blood cells, consists of two proteins, an α- or β-globins. Several monogenic defects can affect the normal production of haemoglobin and lead to haemoglobinopathies, a large, heterogeneous group of inherited disorders of haemoglobin synthesis that comprise thalassemia syndromes and structural haemoglobin variants. Thalassemia syndromes result from diminished or absence of α- or β-globin proteins, leading to α-thalassemia or β-thalassemia, respectively. Structural haemoglobin variants result from alteration of the globin protein itself, leading to its abnormal function. One such structural variant leads to sickle-cell anaemia (SCA), where a point mutation in the β-globin gene leads to its polymerization upon deoxygenation, turning the normally disc-shaped red blood cells into sickle shapes leading to vaso-occlusive crises, a common and painful complication of the disease, where circulation of blood vessels is obstructed by sickled red blood cells. The resulting restriction in the oxygen can lead to severe bone pain, multi-organ damage and potentially stroke and eventually death. According to a World Health Organization report, approximately 5% of the world's population carries trait genes for haemoglobin disorders, mainly SCA and thalassemia. There are huge geographic variations from about 100,000 Americans with SCA to more than 300,000 affected infants born annually in sub-Saharan Africa. To this day, most of these patients are treated with supportive care and chronic transfusion support with its own complications (particularly iron overload). Haematopoietic stem cell (HSC) transplant from a matched-sibling donor can cure both SCA and β-thalassemia effectively. However, availability of matched donors is limited to only a fraction (10%-20%) of patients and is accompanied by potential life-threatening immunological side effects (graft-vs-host disease and/or graft rejection). Therefore, gene therapy by one-time *ex vivo* modification of haematopoietic stem cells followed by autologous engraftment is an attractive new therapeutic modality. After nearly 15 years of failed attempts at replacing the globin gene and its regulatory elements, new techniques using viral vectors have shown encouraging results, with many patients no longer requiring red blood cell transfusions as their total haemoglobin levels in blood now approach normal values. Proof of principle of being able to treat sickle cell disease was also reported in the past decade. Phase 3 clinical trials now under way should help determine benefit/risk/cost ratios to hopefully move gene therapy towards clinical practice. Finally, using the revolutionary CRISPR/Cas9 gene-editing technology, another trial was just given the green light to proceed by the Food and Drug Administration in early October 2018.[9] In this trial, a patient's own stem cells will be modified to produce high levels of foetal haemoglobin (HbF) – a form of haemoglobin naturally present at birth, which is replaced by the adult form of haemoglobin. The goal is to elevate HbF to alleviate transfusion requirements for beta-thalassemia patients.

Retinal dystrophy

Hereditary retinal dystrophies are a broad group of genetic retinal disorders that are associated with progressive visual dysfunction and are caused by mutations in any one of more than 220 genes.

One of them, the RPE65 gene, provides instructions for making an enzyme (a protein that facilitates chemical reactions) that is essential for normal vision. Mutations in the RPE65 gene lead to reduced or absent levels of RPE65 activity, blocking the visual cycle and resulting in impaired vision. The disease happens when patients inherit a mutation (not necessarily the same) from both parents. The hence referred biallelic (with abnormal RPE65 gene on both chromosomes) mutation-associated retinal dystrophy affects approximately 1,000 to 2,000 patients in the United States.

Luxturna, which became the first gene therapy approved in the US to target a disease caused by mutations in a specific gene, works by delivering a normal copy of the RPE65 gene directly to retinal cells.[10] These retinal cells then produce the normal protein that converts light to an electrical signal in the retina to restore a patient's vision loss. Luxturna uses a naturally occurring adeno-associated virus, which has been modified using recombinant DNA techniques, as a vehicle to deliver the normal human RPE65 gene to the retinal cells to restore vision.

Duchenne muscular dystrophy

Duchenne muscular dystrophy (DMD) is the most common fatal genetic disorder diagnosed in childhood, affecting approximately one in every 5,000 live male births. People with DMD progressively lose the ability to perform activities independently and often require the use of a wheelchair by their early teens. As the disease progresses, life-threatening heart and respiratory conditions can occur and patients typically succumb to their disease in their 20s or 30s. However, disease severity and life expectancy vary. DMD is caused by mutations in the dystrophin gene, with 65% being deletions (the rest being duplications or point mutations) that disrupt the open-reading frame (or genetic code structure made of continuous codons that can be translated into a given protein) of dystrophin mRNA, preventing the expression of a functional protein that helps maintain muscles cells intact.

In September 2016, the FDA approved Exondys 51 (eteplirsen) injection, the first drug approved to treat patients with DMD.[11] Though this is limited to a subset of DMD patients, this represents a proof of concept and the first few patients treated had remarkable results with significant increase of functional muscle cells and improvement of motility. This first gene therapy was approved following an accelerated pathway, which makes the drug available to patients based on initial data, though the approval was conditional on completing an uncontrolled efficacy trial by 2021 to confirm long-term safety and clinical benefit in current ongoing studies.

Genetic engineering has produced a wide range of other medical applications, including recombinant DNA drugs, transgenic animals that can produce pharmaceutically useful proteins, methods for the diagnosis of disease, and/or treat a condition using gene therapy to introduce a functional gene that replaces a defective one.

Therapeutic gene transfer or correction holds the promise of providing lasting therapies as in some examples reviewed above, and even cures for diseases that were previously untreatable or for which only temporary, suboptimal treatments or only supportive care were available.

The initial enthusiasm based on some impressive but rare examples of successes was tempered as gene therapy faced several setbacks in the 1990s. Thankfully, gene therapy has been enjoying a comeback over the past decade and will continue to expand its applications and scope. Effective and long-lasting treatments are now being reported from gene therapy trials in a wide range of genetic diseases (including haematological, immunological, ocular and neurodegenerative and metabolic disorders) as well as for the restoration of the immune system in children born with primary immune deficiency.[12]

Thousands of clinical trials for various diseases have occurred or are in progress, with many more in the pipeline. One recent striking example has been reported as the most significant advance in cancer in the past 30 years, leading to the eradication of blood cancers for which all other treatments had failed. This new therapy which will be detailed later uses gene modified T-cells – called chimeric antigen receptor T-cells (CAR-T cells) – and became the first live drug approved by the FDA in August and November 2017.

Examples of *ex vivo* and *in vivo* applications of genetic engineering are summarized in Tables 2A and 2B.

Table 2A: Clinical applications of ex-vivo gene therapies

Target cells	Disease	Comment
T -cells	Adult B-cell acute lymphoblastic leukaemia	Tisagenlecleucel approved for adult patients.[13] Additional studies in adults completed[14] or ongoing.
	Paediatric B-cell precursor acute lymphoblastic leukaemia	Tisagenlecleucel approved for patients up to age 25[15] 81% remission rate within three months, with all patients who had a response to treatment found to be negative for minimal residual disease in the bone marrow.[16]
	Diffuse large cell lymphoma	Tisagenlecleucel approved May 2018[17]
		Axicabtagene ciloleucel approved November 2018[18] 83% responders, with 48% complete responses[19]
	Indolent lymphoma	
	Chronic lymphocytic leukaemia	
	Hodgkin's lymphoma	
	Mantle cell lymphoma	
	Myeloma	
	Glioblastoma	
	Neuroblastoma	
	Breast cancer	
	Sarcoma	
	Lung cancer	
	Gastric cancer	
	Colon cancer	
	Ovarian cancer	
Haematopoietic stem cells	β-thalassemia	
	Sickle cell anaemia	
	Adenosine deaminase deficiency	
	Severe combined immunodeficiency (SCID)	
	Human immunodeficiency virus (HIV)	To render lymphocytes resistant to HIV infection

Table 2B: Clinical applications of in-vivo gene therapies

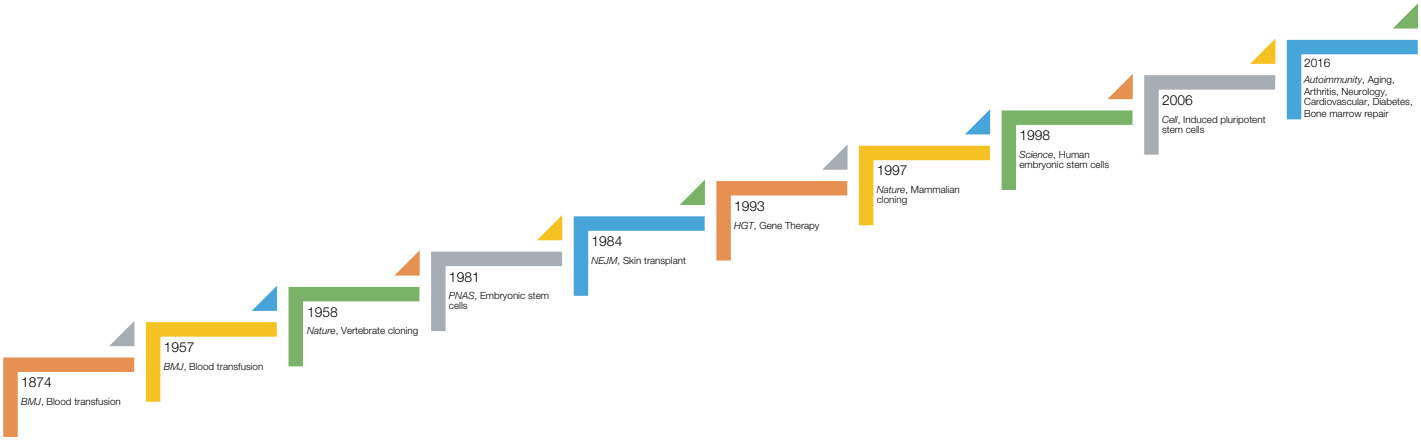
Target cells	Disease	Comment
Central nervous system	Parkinson's disease	
	Spinal muscular atrophy	Spinraza approved in December 2016 by the FDA.[20]
Liver	Haemophilia A	Several compounds with breakthrough designation
	Haemophilia B	
Muscle	Duchenne muscular dystrophy	First drug approved by the FDA in 2016
Retina	Retinal dystrophy linked to RPE65	
Skin	Epidermolysis bullosa	Introduction of normal gene copy into skin stem cells and expansion in the lab before skin graft

Regenerative Medicine and Stem Cells: Improving and Restoring Homeostasis

Though great progress has been made in medicine over the years, evidence-based and palliative treatments are increasingly unable to keep pace with patients' needs, especially given our ageing population. There are few effective ways to treat the root causes of many diseases, injuries and congenital conditions; genetic engineering when feasible might be one of those novel approaches as discussed above, though limited to a small number of conditions so far. In most cases, clinicians can only manage patients' symptoms using medications or devices. Regenerative medicine is a *game-changing area* of medicine with the potential to fully heal damaged tissues and organs. It offers a transformative approach to healthcare, with the potential to not only treat but also cure disease in conditions that today seem beyond repair.

Regenerative medicine is promoting the move towards "*cells as pills*". It refers to the branch of medicine that develops methods to regrow, repair or replace damaged or diseased cells, organs or tissues. Regenerative medicine includes the generation and use of therapeutic stem cells, tissue engineering and the production of artificial organs.[21] The use of live, cell-based therapies in medicine is not a new concept. As shown in the milestone timelines on Figure 1, it spans well over 100 years.

Figure 1: A brief history of the use of live cell-based therapies in medicine



Stem cells research is one of the most fascinating fields of biotechnology. Stem cells can be used to recreate other specialized cells, opening possibilities to grow, repair and replace damaged or diseased tissues. The first successful allogeneic human haematopoietic[22] stem cell transplant took place in 1968 (in a case of severe combined immunodeficiency patient) and has since been performed in hundreds of thousands of patients worldwide. Similarly, full organs' transplants from donors have helped save lives for decades. However, advances in developmental and cell biology, immunology and other fields have unlocked new opportunities to refine existing regenerative therapies and develop new ones. The expanding potential for regenerative medicine will likely apply across medicine, while emerging applications are entering the clinic with some examples detailed in Table 3.

Table 3: Successes and promises in regenerative medicine

Restore the homeostasis of the immune system
The use of **autologous haematopoietic stem cell** (HSC) **transplant** after high-dose chemotherapy has been well established and is now even done on outpatients. HSC helps the patient recover from side effects and tissue damage of high-dose anti-cancer therapy mostly in the management of blood cancers. Nevertheless, this technology continues to find new clinical applications. For example, recent results from an international clinical trial showed that high-dose immunosuppressive therapy and subsequent autologous HSC transplants are effective in inducing long-term sustained remissions of active relapsing-remitting multiple sclerosis.[23] In this trial, only 6% of patients treated with HSCs relapsed, compared to 60% in the untreated control group. **Donor-based bone marrow and stem cells transplant**: the first proof of benefit of this form of cell therapy in leukaemia was performed over 50 years ago by Don Thomas in Cooperstown, New York state, who was awarded with the Nobel Prize in Medicine for a procedure now used throughout academic centres worldwide. Since then, allogenic stem cell transplants have helped save lives of patients with refractory cancers such as leukaemia, lymphoma and also some haemoglobinopathies as mentioned above. However, they are often associated with the risk of acute or chronic graft versus host disease (GVHD), a debilitating condition with high mortality. Mesenchymal stromal cells (MSCs) are a type of adult stem cells residing in bone marrow, adipose tissue, umbilical cord blood and many other tissues. MSCs, with self-

renewal potential and trans-differentiation capability, can be expanded *in vitro* and directed to various cell lineages with relatively less efforts. MSCs have secured conditional approval in 2012 to treat children with GVHD in Canada and New Zealand and, latterly, approval in Japan was obtained as well (not yet in the US). Numerous trials are ongoing into other potential roles of MSCs in other diseases.

Auto-immunity: Besides GVHD (a form of induced autoimmune disease), MSCs have also been looked at for other autoimmune diseases such as Crohn's disease and osteoarthritis as well as Type 1 diabetes (T1DM). It is well established that in T1DM immune cells attack the beta cells in the islets of Langerhans (pancreatic islets). However, Type 2 diabetes (T2DM), although considered to be a disease related to insulin resistance, has also been shown in recent studies to be linked to immune dysfunction. MSCs can differentiate and replace the dead cells as well as secrete stimulant factors to activate surrounding cells in the microenvironment, enhancing tissue repair and exert immunomodulatory capabilities. MSCs transplants in preclinical trials and preliminary results in clinical trials for T1DM and T2DM have shown improvement in diabetes without adverse side effects.[24] Ongoing larger trials will hopefully refine the best timing for such approaches.

Chronic inflammation: Regenerative medicine also has applications for addressing chronic inflammation by altering the microbiome. Monoclonal microbials are orally delivered pharmaceutical compositions of specific strains of naturally occurring microbes derived from a single clone. They are designed to act on the gut-body network. In preclinical studies specific monoclonal microbials can down-regulate or up-regulate immune responses throughout the body by acting on the gut-body network with naturally evolved pharmacology.

Regenerative medicine in neurology

Central nervous system diseases (CNS) are neurological disorders affecting the function of the brain. These include Parkinson's, Alzheimer's, Huntington's, multiple sclerosis and amyotrophic lateral sclerosis or ALS among others. Parkinson's disease is a progressive disorder that affects roughly 2% of people aged 65 and older. It is triggered by the death of neurons from a brain region called Substantia Negra, for reasons still not well understood. These neurons control a large number of target neurons throughout the brain and are particularly involved in the control of movement and muscle tone. Patients start often with tremor, rigidity and difficulty in motion. For years, Parkinson patients have been treated with supplementation therapy, Levo-Dopa, which can improve motor symptoms. Over time, however, drugs become less effective and are associated with side effects such as involuntary movements (dyskinesias).

Until the late 1970s, it was generally believed that repairing the central nervous system in humans, which had never been possible in the past, would never be possible in the future. However, two articles with obvious clinical implications were published in 1979 showing that intracerebral grafts of foetal mesencephalic dopamine-rich tissue in rats could ameliorate signs of experimental Parkinson's disease. The findings in the animal models raised the possibility of a novel therapeutic approach for Parkinson patients based on replacing the dead dopaminergic neurons by healthy ones through transplants.

Restore skin homeostasis

Evidence of skin repair (as shown by wound healing) supported the development of autologous cultured epidermis transplants, a now long-established approach. Notable progress has recently been made in the **treatment of skin-blistering disorders by gene correction of epidermal cells**, followed by their expansion in culture and subsequent transplant. In a recent world first, this graft technique was used to almost completely replace the skin of a child with epidermolysis bullosa.[25]

Junctional epidermolysis bullosa is a severe and often lethal genetic disease caused by mutations in genes encoding the basement membrane component. Surviving patients with epidermolysis bullosa develop chronic wounds to the skin and mucosa, which impair their quality of life and lead to skin cancer and and overall devastating, life-threatening condition. In that proof of concept autologous gene-corrected keratinocytes from a patient with epidermolysis bullosa could be cultured into large epidermal grafts *in vitro* and applied to the patient's body surface. The graft showed normal physiology during 21 months of follow-up. Clonal tracing showed that the human epidermis was sustained by a limited

number of long-lived stem cells that can extensively self-renew *in vitro* and *in vivo* and produce progenitors that replenish terminally differentiated keratinocytes. This study provides a blueprint that could be applied to other stem cell-mediated combining *ex vivo* cell and gene therapies.

Regenerative medicine in cardiovascular diseases

Humans regenerate many of their tissues – including skin, blood, liver and intestinal mucosa – routinely, efficiently and often perfectly. Skeletal muscle regenerates remarkably well; every time we strain a muscle, muscle stem cells repair the injury and this is a key component of the conditioning associated with exercise training. This is not the case for the human heart, or at least in very limited fashion. A revolution in stem cell biology has led to an explosion of interest in therapies that can awaken the regeneration potential in patients. In the past decade alone, we have learned that any cell type from any patient, including cells from a blood sample or skin biopsies, can potentially be reprogrammed into human-induced pluripotent stem (iPS) cells and that a patient's own stem cell can generate billions of new cells of a variety of differentiated cell types, including cardiomyocytes, endothelial cells and neurons. The global impetus to identify curative therapies has been fuelled by the unmet needs of patients in the context of a growing heart failure pandemic and an enormous worldwide burden of cardiovascular disease.

To date, regeneration trials in patients with cardiovascular disease have used stem cell-based therapy in the period immediately after myocardial injury, in an attempt to halt progression towards ischemic cardiomyopathy, or in the setting of congestive heart failure, to target the disease process and prevent organ decompensation.[26] Promising Phase 2 data led to larger trials of "first-generation" cell-based therapy. Worldwide, several thousand patients have now been treated using autologous stem cell-based therapy. The safety and feasibility of this approach have been established; pitfalls have been identified (cell subtypes, quality variability, persistence of modified stem cells and clinical benefit duration) as well as optimization of procedures envisioned. Ongoing trials of "next-generation" stem cell-based therapies targeting cardiovascular disease will hopefully refine their benefit and indications and help reassure on their safety and risk at scale, the details of which are beyond the scope of this review.

Regenerative medicine in orthopaedics

Articular cartilage forms the articulating surface of synovial joints. Along with the synovial fluid, it facilitates near frictionless movement in healthy joints. Injuries to articular cartilage in the knee are frequent and can lead to severe osteoarthritis, which is expected to affect well over 25% of the adult population by 2030. Several relevant tissues, such as cartilage, meniscus and intra-articular ligaments, do not heal, and even bone, which normally regenerates spontaneously, can fail to mend. So far, treatment is either purely pain control and supportive measures or surgery with joint replacement. Though such surgeries have improved dramatically in their complications and functional outcome, the results vary among patients, new joints need to be replaced over time and most patients still experience some residual chronic pain. Regenerative medicine has great potential for cartilage repair but is still in its infancy.

There is a zoo of stem cell therapies advertised, and private – poorly controlled – clinics are giving the field overall a bad reputation. A number of approaches has been tested, from platelet-rich plasma (to reduce inflammation), MSCs (healing as reviewed above), autologous stem cells derived from bone marrow or body fat to stem cells-derived exosomes (vesicles released by cells to communicate with each other), which have shown benefit when applied on to ageing cells and tissues.[27] It is still early but certainly proof of concept has been demonstrated in patients with documented cartilage or tissue repair and functional improvement in the clinic. Though numbers remain small, specialists say that "while drugs and devices have helped us through the past 60 years with arthritis, it will probably be biologics, in an injectable form, that will be necessary to help us through the next 60 years"

Regenerative medicine in organ replacements

Organ transplant: The therapeutic modality of choice in end-stage organ failure may be referred to as one of the greatest achievements in the history of medicine. However, since the beginning of organ/tissue transplants, organ shortage has been the main challenge. For example, kidney transplants currently represent the gold standard for renal replacement therapy in patients affected by end-stage renal disease. It dramatically improves patient survival, quality of

life and is cost-effective when compared with long-term maintenance with peritoneal or haemodialysis. According to the *2018 US Renal Data System Annual Data Report*, life expectancy from the time dialysis is initiated is approximately 10 years for patients aged between 40 and 44 and just under six years for those between 60 and 64. These figures are far surpassed by the increased expected remaining lifetime after a kidney transplant, which is about 28 years for patients between 40 and 44, and over 14 years for those between 60 and 64.[28]

As per the Global Observatory on Donation and Transplantation (GODT) affiliated to the World Health Organization, the total number of 135,860 solid organs reported to be transplanted in 2012 represented only a 7.25% increase from 2015 and surprisingly less than 10% of global needs.[29] Similarly, at the end of 2016, over 81,000 candidates were waiting for a kidney in the US, whereas only 19,301 kidney transplants were performed during the calendar year.[30] Despite a variety of approaches implemented to expand the organ donor pool including live donation, international efforts to expand deceased donor donation and split donation among others, the gap between increasing demand and supply of organs is still widening.

Transplants and regenerative medicine share the same essential goal, to replace or restore organ function.[31] Regenerative medicine holds the promise of engineering damaged tissues and organs via stimulating the body's own repair mechanisms to functionally heal previously irreparable tissues or organs. It also includes the possibility of growing tissues and organs in the laboratory and safely implants them when the body cannot heal itself. Progress made in cell and stem cell biology, material sciences and tissue engineering enable researchers to develop cutting-edge technology, which has led to the creation of non-modular tissue constructs such as skin, bladders, vessels and upper airways. Engineering of organs with functioning units and vascular supply is much more complicated and there is long way to go to achieve this goal at scale and with reasonable and affordable costs. The idea of creation of bioengineered solid organs will optimistically relieve the main and grave concerns of organ transplants, organ shortage and complications of life-time immunosuppressive therapy.

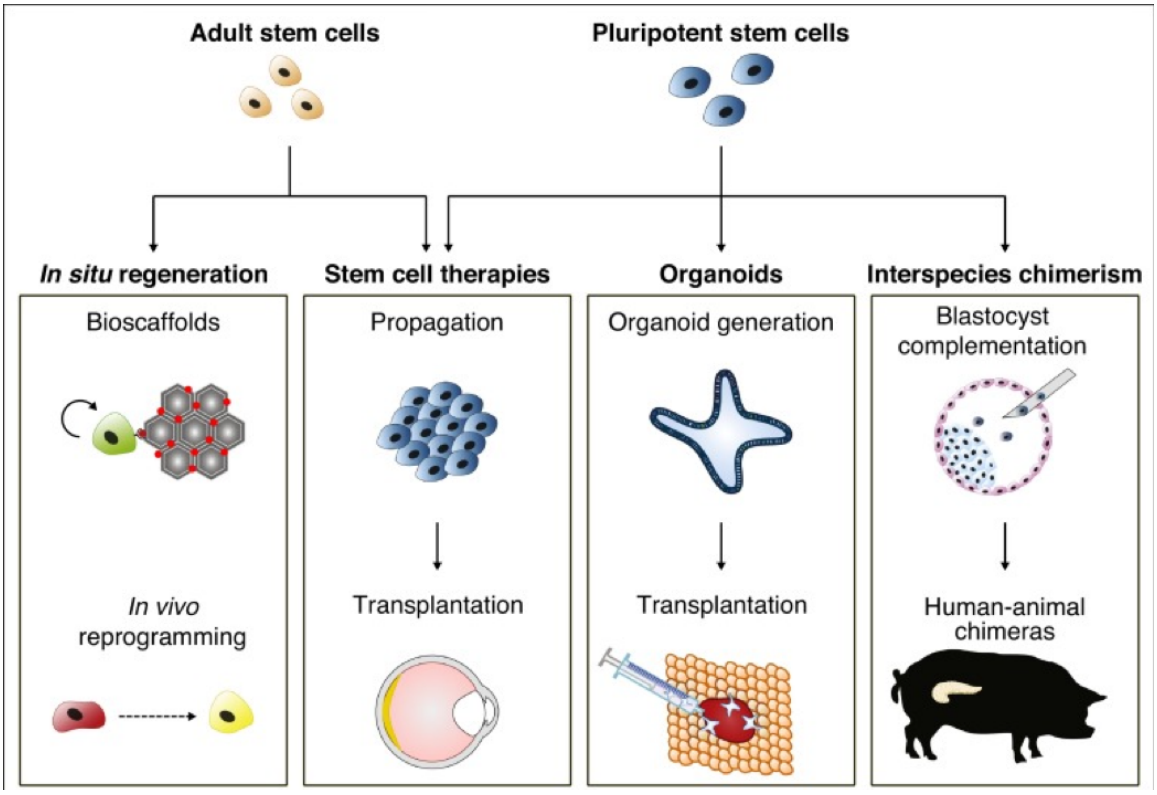
Table 4: Other applications of regenerative medicine

Field	Condition/Tissue	Comment
Pulmonary health	Mesenchymal stromal cells have shown benefit in idiopathic pulmonary fibrosis	Larger trials needed
Cerebral palsy and autism	Autologous cord blood therapy has shown preliminary encouraging results in children with neonatal brain injury, cerebral palsy and autism	Ongoing studies at Duke University
Patients with acquired and genetic brain diseases	Preclinical and early clinical studies show benefits from manufactured microglial oligodendrocyte-like cells from cord blood	
Ageing	Tissue repair: bone marrow-derived mesenchymal stem cells, stem cell-derived extracellular vesicles (exosomes, secretomes) are being tested as potential therapeutic tools for tissue repair and a potential solution for ageing and tissue regeneration	Preclinical, but promising with mice treated with those stem cells showing very little signs of ageing at four years.
Bone repair	*Ex vivo* growth of bone	

Marching Towards the Future: Current Strategies to Expand the Potential of Regenerative Medicine

Regenerative medicine borrows sometimes from genetic engineering to reprogramme cells but overall there are now multiple sources of cells and ways to generate materials for regenerative medicine as shown on Figure 2.
Somatic stem cells can be targeted *in situ*, through the application of bio scaffolds seeded with pro-regenerative agents to activate endogenous repair mechanisms.[32] Alternatively, tissue-resident cells can be reprogrammed from a pathophysiological state; for example, by reprogramming liver fibroblasts into liver cells called hepatocytes in fibrotic liver,[33] or to an alternative functional state (for example, liver cells into pancreas progenitor).[34] Adult, embryonic or induced pluripotent stem cells can also be transplanted to enhance regeneration. This may include *ex vivo* expansion and gene editing to correct pathogenic mutations. The transplant of organoids show promise as a strategy to improve regeneration.[35] Finally, the generation of human-animal chimeras could facilitate the production of entire human organs. Not surprisingly, such approaches generate controversy and challenges as shown by ongoing work in pigs to grow human organs. Such xenogeneic transplant from pigs to humans involves high immune incompatibility and a complex rejection process, issues that might be tackled in the future.[36]

Figure 2: Strategies to expand the potential of regenerative medicine



Source: Clarke, G., Harley, P., Hubber, E-L., Manea, T., Manuelli, L., Read, E., Watt, F.M., "Bench to bedside: Current advances in regenerative medicine", Current Opinion in Cell Biology, vol.55, 2018, pp. 59-66

Immunotherapy

Immunotherapy is defined by *Nature* as the treatment of disease by inducing, enhancing or suppressing an immune response.[37] The concept of taking advantage of the immune system to help fight cancer goes back well over 100 years ago. The observation of tumour regression after local skin infection at the surgical site by Coley over 100 years ago led to the first rationale for immunotherapy. Up to the 1950's the Coley's toxin (mixture of killed bacteria) was used with some clear successes (though criticized at the time by many), including some sarcoma patients who lived a full life up until their late 80s.

Since then immunotherapy has gone through phases of enthusiasm and scepticism for decades followed by a true renaissance phase which started about 10-15 years ago to become a very rapidly expanding field and represent now the 5th modality of cancer therapy after (and in order) surgery, radiation, chemotherapy and biologicals/targeted therapies.

Progress in the understanding of cell biology and cancer have clearly demonstrated the ability of the immune system to eliminate naturally occurring cancer cells through a phenomenon called immunosurveillance. Patients with immunosuppression after a bone marrow transplant from a donor or organ transplant can develop rapidly growing tumours. In particular, aggressive β-cell lymphomas are usually (but not always) driven by reactivation of latent viruses in our system such as EBV, the well-known mono virus which remains dormant after initial contact/infection that occurs early in life, usually before 10-20 years old. When possible, particularly after a bone marrow transplant, stopping the immunosuppressors leads to regression of the lymphoma, bringing another proof of evidence of the power of immunotherapy.

Over 30 immunotherapy drugs and indications were approved in the past four years in the US. Ongoing research will help predict which patients would benefit most from these therapies, understand the mechanisms of resistance involved and refine the best timing to use these new forms of therapy. As seen already, in some cases they will replace chemotherapy and/or help prevent recurrence after first-line therapy in patients with high-risk disease.

Immunotherapy after over a century of research will become the cornerstone of oncology and, impressively, will likely apply to almost all types of cancers. Other aspects of immunotherapy are beyond this review, but will also have an impact on autoimmunity and some aging-related diseases.

Without covering all strategies, several key approaches are described with some examples in Table 5.

Table 5: Successes and promises in immunotherapy

Monoclonal antibodies (mAb) can target and attach to certain proteins on cancer cells, enabling the immune system to recognize and destroy those cells more easily. One of the most commonly used, **mAb**, is an anti-CD20, called rituximab, approved by the FDA in 1997,[38] which has changed the treatment of B-cell malignancies (both lymphoma and leukaemia). Since then, the second and third generation of antibodies have been approved in lymphoma multiple myeloma and leukaemia but also across solid tumours.
Using fragments of proteins from tumours to induce an immune response: These vaccines are typically used with adjuvants to prime the immune system or loaded in immune cells type, such as dendritic cells, which are critical in initiating the immune response. One of them became the first cellular immunotherapy approved for cancer: sipuleucel-T (Dendreon) in prostate cancer in 2011. Other vaccines have been developed in lymphoma and leukaemia (including AML) with mixed results so far. New generations of vaccines are very promising, particularly recent work from Ron Levy's laboratory in Stanford University using a model of intratumour given vaccine.[39] This model is highly innovative as local immunotherapy induces regression of systemic tumours in spontaneous cancers. Trials in humans are currently under way.
Cell therapy: Donor stem cell transplant was the first form of cell therapy vaccine in the early 1980s. It has been performed in hundreds of thousands of people around the world establishing the proof of graft versus tumour effect with many patients cured. This proof of anti-tumour effect has been reinforced by the evidence that donor lymphocytes infusion (DLI) given to patients who relapse after donor-based stem cell transplant can induce again durable remission. To this day, allogenic stem cell transplant is the only chance for a cure for many patients with refractory blood cancers.

Antibody drug conjugates (ADCs) feature both the mechanism of monoclonal antibodies reviewed above but also carry cytotoxic molecules or toxin on their "tails", which can kill cancer cells. Many of these ADCs are in the pipeline. The most well-known is brentuximab vedotin, an anti-CD30 approved in several types of Hodgkin and non-Hodgkin lymphomas, or anti-HER2 Pertuzumab in breast cancer.

BITE: Bi-specific T-cell engagers (BiTEs) are a new class of immunotherapeutic molecules that can enhance the patient's immune response to tumours by retargeting T-cells to tumour cells. BiTEs have been developed that target several tumour-associated antigens for a variety of both haematological and solid tumours. Blinatumomab was approved in relapsed/refractory acute lymphoblastic leukaemia in adults based on impressive Phase 2 data, with most patients achieving a complete molecular response.[40]

Checkpoint inhibitors represent one of the most exciting venues in immunotherapy. Progress in understanding both basic immunology and cancer cell biology confirmed that, early on, cancer cells learn how to hide or suppress the immune system allowing the cancer to continue to progress. The dialogue between the cells of the immune system and their targets (such as virus-infected cells, bacteria or even cancer cells) is highly regulated particularly though a system of checks and balances called checkpoints.

Many of those receptors have been identified, among them PD1 on T-lymphocytes and PDL1-PDL2 on tumour cells. These function as sort of gatekeepers of the immune response and can be altered in cancer which lead to immune tolerance (i.e. no rejection of cancer cells). The development of monoclonal antibodies targeting, for example, PD1 (nivolumab, pembrolixumab) has allowed us to unleash the immune system which has been revolutionizing cancer care particularly in solid tumours such as lung cancer, head-neck cancer, some GI cancers, bladder cancers and melanoma, to name a few. The results are so impressive that patients with brain metastases of melanoma who would often be referred to a hospice can now frequently be cured.

Many checkpoint inhibitors are being evaluated, with over 300 ongoing studies in the US. This very important discovery of checkpoint inhibitors and their implications for cancer patients led to the Nobel Prize in Medicine for both Jim Allison and Tasuku Honjo in October 2018.

Oncolytic viruses (OVs) are another form of therapy that can help build up immunotherapy. Viruses can selectively replicate inside and kill cancer cells helping to induce immunity. To date, only one oncolytic virus, talimogene laherparepvec (T-VEC), has been approved by the FDA. This particular oncolytic virus T-VEC is based on herpes simplex virus type 1 and has been modified to include a gene that codes for GM-CSF, a protein that stimulates the production of immune cells in the body. A number of other OVs are being evaluated as potential treatments for cancer in clinical trials.

Chimeric antigen receptor T-cells (CAR T-cells) are without doubt the most exciting development in the evolution of immunotherapy – and the biggest development in cancer in 30 years. For CAR T-cells, immune cells (T -cells) are collected from the patient's peripheral blood and then genetically modified by introducing a gene that will force the cells to recognize and attack cancer cells. The modified cells are expanded in the laboratory and reinfused to the patient two to three weeks later after the patient receives some mild chemotherapy (which "preps" the patient's own milieu to let those infused cells expand and kill cancer cells better[41,42]).

The first proof of concept for such therapy was in Emily, a young patient with refractory acute lymphoblastic leukaemia. She received anti-CD19 CAR T-cells in 2013, under the care and science of Carl June at the University of Pennsylvania in Philadelphia, and remarkably has remained in remission ever since and is likely cured.

In 2017, two CAR T-cell therapies were FDA-approved: for aggressive relapsed/refractory B-cell non-Hodgkin lymphoma and paediatric relapsed B-cell acute lymphoblastic leukaemia (ALL) (up to the age of 25). There are now over 600 ongoing studies for all kinds of blood cancers and studies starting in solid tumours as well.[43,44] These novel forms of cell therapy are game-changing but bring new challenges. The toxicity profile of these therapies (particularly cytokines release syndrome, a type of "immunological storm" seen three to five days post infusion) and neurotoxicity (due to penetration of the brain by activated T-cells) explain why only experienced and certified centres are allowed to deliver these therapies.

In addition to access, the cost is prohibitive. The price tag ranges from $375,000-$475,000 just for the CAR T-cells themselves plus the cost of administration and managing potential complications, which can easily reach well over $2 million in total for one patient in the US. This is currently a major issue as payers, including Medicare, are not ready to shoulder the financial burden of these therapies. Though this is potentially a finite therapy with some patients likely cured, costs will have to come down. This will happen thanks to new forms of off-the-shelf CAR-T, less toxic CAR-T cells or just plain competition given the number of companies entering the field.

Precision Medicine

Some Definitions

Medicine improves in gradual steps and quantum leaps. In the 20th century, the conceptual framework for medicine was based on *the germ theory of disease*, which was developed during the 19th century by Pasteur. The fundamental assumption was that acquired diseases were caused by a single pathologic factor (for example, bacteria) that results in a complex syndrome, but can be treated by focusing on the etiological agent. At the same time, disease taxonomy (that is, disease description, nomenclature and classification) was built on tissue pathology, and the diagnosis of a disease was made on the basis of the identification of pathology within a tissue sample or by using surrogate signs and symptoms. If a "germ" or other single etiological factor was not identified, the disease was defined by *the type of pathology* (for example, inflammation) rather than the etiology. This model proposed by Flexner in the early 1900s was designed to identify single aetiologies for complex syndromes and served as a framework to practise medicine for all of the last century. This approach continues to be taught in medical schools today.

The explosion of clinical and basic research publications in the last half of the 20th century resulted in data overload for physicians, which led to the emergence of *evidence-based medicine*. This new analysis framework was developed by clinical epidemiologists in the early 1990s to evaluate, synthesize and present clinical research reports in a standardized fashion that could be understood and acted on by clinicians and policy-makers to support guidelines. In oncology, for example, ASCO[45] or NCCN[46] guidelines serve to this day as the main references for physicians in their daily practice of medicine. This new approach was accompanied by an increasing support for outcome research and quality measurements – including enforcing electronic health records (EHR) and electronic medical records (EMR) implementation – to improve decisions and start reining in the rapidly rising costs of medicine by streamlining and aligning treatment decisions.

In recent years, technological advances in genomics, particularly since the human genome sequencing project, have improved our understanding of tumour biology, which led to an acceleration in the development of new biological targeted agents. Numerous initiatives led by the National Institutes of Health (NIH) in the US, particularly the Cancer Genome Atlas Network, have played a central role in elucidating the landscape of genomic alterations that drive carcinogenesis across multiple malignancies, providing a critical foundation for novel therapeutic approaches. The results of these massive genetic, epigenetic and transcriptomic analyses have also revealed the *impressive biological heterogeneity of cancer*, providing a rationale for moving away from the current approach of "one size fits all" therapies.

The tailoring of disease treatment to a specific person, taking into account their genetic and biological make-up, the environment in which they live and how they live their life is referred to as *precision or personalized medicine*. These terms are often used interchangeably, though their definition remains hotly debated by experts. This report keeps to the aforementioned definition of precision medicine – the one adopted by the World Economic Forum's Centre for the Fourth Industrial Revolution.[47]

Historical Perspectives of Precision Medicine

The field of molecular biology emerged as a well-defined field after the discovery of the double helical structure of DNA by Watson and Crick in 1953, with researchers focused essentially on the elucidation of mechanisms: how does DNA replicate, how do proteins get synthesized or how do genes get regulated? This research area benefited from widespread acceleration thanks to recombinant-DNA techniques in the early 1970s. The key to understanding cells at the time was to take them apart, identify their molecular components and then study how these components interact, a few at a time, to produce functional effects. The notion was that the sum of all these effects would provide a complete picture of the "complex cellular puzzle"; i.e. of how cells and organisms work.

Meanwhile, emergence of more global approaches such as mapping the genome of yeast or E. coli emerged, though these were looked at sceptically by geneticists at the time. Charles DeLisi and Robert Sinsheimer, both visionaries, started the concept of the human genome project – perceived by many initially as an "*unnecessary endeavour*". Nevertheless, the International Human Genome Sequencing Consortium was established and funded in 1990. This tremendous effort – over 10 years and at a cost of $3 billion – led to the publication of the first draft of the human genome in *Nature* in February 2001 (with the finalized version two years later in April 2003), showing among other things surprisingly fewer genes than expected in humans (22,000 vs some estimates of up to over 140,000 previously). Many other organisms have been sequenced ever since, helping to understand evolution and also opening new possibilities, as for the first time we could also sequence entire cancer cells and understand better the drivers of cancer.

Technological advances have also dramatically reduced the time (now feasible in a few hours) and cost (now less than $1,000 per genome) of genome mapping, leading many to believe this could be done in regular practice to inform decisions. Over the past few years, there has been a growing recognition of precision medicine by clinicians, health systems and the pharmaceutical industry, as well as by patients and policy-makers, culminating in a Precision Medicine Initiative (PMI) under President Obama, announced in 2015, to accelerate progress towards a new era of precision medicine.[48] The initiative, now called *All of Us Research Program*, has a near-term focus on cancers and a longer-term aim to generate knowledge applicable to the whole range of health and disease.[49] This cohort is a landmark longitudinal research effort that aims to engage 1 million or more US participants to improve our ability to prevent and treat disease based on individual differences in lifestyle, environment and genetics. In addition to capturing clinical health and healthcare data, samples from blood and stools from participants in the *All of Us* cohort will be collected for extensive correlative and screening studies, including sequencing. For example, a genome-wide association study (GWAS) in this observational study will likely help identify genetic variants or markers in individuals that might predict a trait or disease risk.

Examples of Precision Medicine in Practice

Using genetic information to individualize medication or tailor therapy, i.e. pharmacogenomics, is already part of routine clinical practice. A few examples spanning several areas of medicine will be detailed in Tables 6 and 7.

Table 6: Precision Medicine in practice

Cystic fibrosis is a genetic disorder that leads to a chronic multisystem disease consisting of chronic sinopulmonary infections, malabsorption and nutritional abnormalities. It is the most common autosomal recessive life-shortening disease among Caucasians in the US and lung involvement is the major cause of morbidity and mortality.[50] Cystic fibrosis is caused by mutations in a gene on chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which functions as mostly a chloride and bicarbonate channel that controls the movement of fluid into and out of epithelial cells.

Since the identification of the gene 25 years ago, over 1,900 CFTR mutations and variants have been identified, although over 80% of people with cystic fibrosis in the US possess at least one copy of the most common mutation, F508del. While advances in gene therapy and gene editing systems might help treat the basic defect in all patients, model systems of airway and intestinal epithelial cells from individuals with cystic fibrosis to test CFTR modulators might help further customize care once a broader range of CFTR drugs becomes available.

Warfarin, the most widely used worldwide oral anticoagulant for the treatment of thrombotic disorders, requires intensive monitoring and dosage adjustments based on target international normalized ratio (INR) to avoid drug-related complications, which represent the most common cause of emergency department visits and hospitalizations for adverse drug events. Warfarin is metabolized by cytochrome P450 2C9 (CYP2C9) in the liver, with two single nucleotide polymorphisms (SNPs) reported associated with reduced warfarin metabolism and lower dose requirements. The pharmacological target of warfarin is vitamin K epoxide reductase (VKORC1), which controls the formation of vitamin K-dependent clotting factors. A common variant of VKORC1 has been shown to lower the warfarin target protein expression, leading to warfarin sensitivity and lower dosing requirements. The benefit of adjusting warfarin (to remain within therapeutic range) based on PGx algorithm was confirmed in a randomized trial[51] Further evaluation of the decreased risk of long-term complications (particularly haemorrhage) or in the prevention of deep venous thrombosis recurrence is the subject of ongoing trials.

Numerous examples of precision medicine can illustrate the expectations placed in **oncology as the leading field for implementation of precision medicine**.

The example of chronic myeloid leukaemia (CML) established a new paradigm in oncology and medicine. CML is caused by a single aberrant protein (bcr-abl kinase). When CML was diagnosed in patients, their life expectancy at the time was about four years. Some patients could undergo an allogenic stem cell transplant, though with severe toxicity and a mortality date of about 40%. The development of targeted agents against bcr-abl changed the field overnight. Imatinib, the first kinase inhibitor developed, showed in a Phase 1 trial minimal toxicity while 53 of 54 patients went into unprecedented complete haematological response.[52] Five years later, 83% of those patients remained disease-free, compared to a historic rate of overall survival of about 30%. Second- and third-generation tyrosine kinase inhibitors (TKI) have been introduced since to prevent or counteract the problem of drug resistance that may arise in a small proportion of patients. These “new” TKI are more potent molecules but have been associated with more serious side effects and complications but still have led to durable responses and the rare need for stem cell transplants. In fact, patients achieving stable optimal responses to TKI therapy are predicted to have the same life expectancy as the general population.

Furthermore, the depth of responses seen with these TKI in CML is such that some patients have been able to even stop therapy after three years, with almost half remaining in remission without therapy (the other half still typically doing well though they must resume their TKI therapy). Nowadays, it is part of routine evaluation of CML patients to test them for primary resistance or acquired resistance to TKI to help tailor therapy. Unfortunately, CML stands out as a unique example of success, likely explained by the high dependence of the cancer cells on this predominant oncogenic protein, by opposition to a much more complex genetic picture and genetic instability in most other cancers. Nerveless CML is a perfect example of pharmacogenomics and implementation of precision medicine.

Table 7: More examples of Precision Medicine applications across medicine

Field	Disease	Examples of PM use
Oncology	Lung cancer	Epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) are the two most prominent mutations leading to replace chemotherapy with tyrosine kinase inhibitors
	Melanoma	BRAF mutations testing
	Hairy cell leukaemia	BRAF mutations testing
	Breast cancer	ER/PR/HER2 mutations testing
		Oncotype: TAILORx trial showed that over 50% of women with the most common form of breast cancer do not need chemotherapy[53]
Immunotherapy	Checkpoint inhibitors	PD1/PDL1 expression affects response to checkpoint inhibitors such as nivolumab, pembrolizumab and ipilimumab, among others
		Mutations burden load correlates with response to checkpoint inhibitors
		T-cell infiltrates correlate with outcome in solid tumours receiving checkpoint inhibitors
		FDA-approved pembrolizumab in patients with microsatellite instability (MSI)-high or mismatch repair (MMR)-deficient solid tumours, as a first across tumour types
		Microbiome impacts +++ response to checkpoint inhibitors
Haematology	Thrombosis	Individuals with Factor V Leiden to avoid prothrombotic drugs
Infectious diseases	Bacterial infections	Drug sensitivity and molecular testing to help refine antibiotics regimens
	HIV-1 infection	CD4+ T cells, HIV viral load and resistance panel to highly active antiretroviral therapy
	Hepatitis C	Viral load, resistance panel to adjust therapy
Cardiovascular	Clopridogel	CYP2C19 polymorphisms affect metabolism of antiplatelet agent clopidogrel impacting antiplatelet treatment recommendations for prevention and treatment of stroke and infarcts
	Statins	Multiple polymorphisms impact the efficacy or toxicity profile of statins
Neurology	Alzheimer's/dementia	Major genetic risk factor for Alzheimer's in individuals with a specific copy of the APOE gene
Psychiatry and behavioural sciences	Alcohol-use disorder	GRIK1 polymorphism affects response to Topiramate used to reduce and stop drinking
	Smoking cessation	CYP2A6 genotype impacts nicotine clearance and smoking dependence

Challenges, Limitations and Promises of Precision Medicine

Though the impact of the examples noted above can vary, it is not surprising that together they have helped build up the enthusiasm for precision medicine as a highly promising and universal solution for the future. In fact, personalized medicine and now precision medicine have become a catchphrase, consistent with the "*individualization*" of society, as a promise that each individual will be able to receive the right treatment for their specific medical need at the right time and at the right dose. The European Alliance for Personalised Medicine goes even further and includes personalized prevention, while others have suggested the term "*stratified medicine*", which seeks to identify groups of patients with specific molecular characteristics or other determining factors to predict prognosis and response to therapy.

Precision medicine focuses on the optimization of therapeutic outcomes by considering individual patient characteristics. However, challenges have mounted from the enormous amount of data generated, the diversity of sources and need for integration, quality of data and analysis, in addition to patient privacy and coordination across points of care and patients' ecosystem (including data obtained from mHealth on mobile devices).

That said, the increasing importance of real-world data will need to be supported by policy-makers by facilitating access and sharing of information, which would greatly enhance progress and discovery and help evaluate the true clinical benefits outside trials. Similarly, the drug approval process needs to be adjusted to support the design of small trials based on patients' similarities (not just molecular) with early conditional approval (based on efficacy) while using real-world data to confirm both toxicity profile and clinical benefit. This also calls for policy-makers to facilitate collection and access to tissue, a key obstacle in the implementation of precision medicine and the development of critical companion diagnostics tests.

Thankfully, several initiatives are emerging to address these challenges. One notable example is the World Economic Forum Precision Medicine portfolio, led by the Forum's Centre for the Fourth Industrial Revolution, which aims to support the development of policy frameworks and governance protocols to realize the societal benefits of, and mitigate the risks from, precision medicine.

Precision Medicine: A summary

- There is no doubt that many of the key ingredients are available today to make significant progress in the implementation of precision medicine.
- Precision medicine is not only about finding new targeted therapies. It also identifies what the best sequence of care is for a given patient – not a trivial question knowing the increasing number of options available today.
- Precision medicine applies to every subspecialty in medicine and likely to prevention. It is still early days, but the emergence of systems medicine might help implement at scale P4 medicine – predictive, preventive, personalized and participatory – with the goal of quantifying wellness through the full continuum of care. The stakeholders are not aligned on this, particularly because they see it as an increased cost at least initially. However, the development of more rational or stratified medicine – a key first step for precision medicine – will help improve individual outcome by reducing variance and cost, a central issue to the survival of advanced health and healthcare systems.
- Policy-makers need to support the changes required to accelerate precision medicine, particularly access to and sharing of data, drug development, access to tissues, and biomarkers approval.

Enhancing Human Health for Improved Wellness

Nanotechnology

Nanotechnology encompasses a number of emerging technologies dealing with structures that have or involve dimensions of less than 100 nanometers (10^{-9} metres). Essentially, nanotechnology refers to the creation of structures exhibiting novel and significantly improved physical, chemical and biological properties, phenomena and processes at the nanoscale size. When applied to health, nanotechnology is often associated with biotechnology, information technology, and neuroscience and technologies.

Nanotechnology is found everywhere. More than 1,700 consumer products containing nanoparticles have been introduced into the marketplace since 2005. For example, titanium dioxide nanoparticles are now widely used in food (notably chewing gum, sweets and candy), dietary supplements and personal care products (notably sunscreens and toothpastes), sometimes accounting for as much as 10% of their total weight.

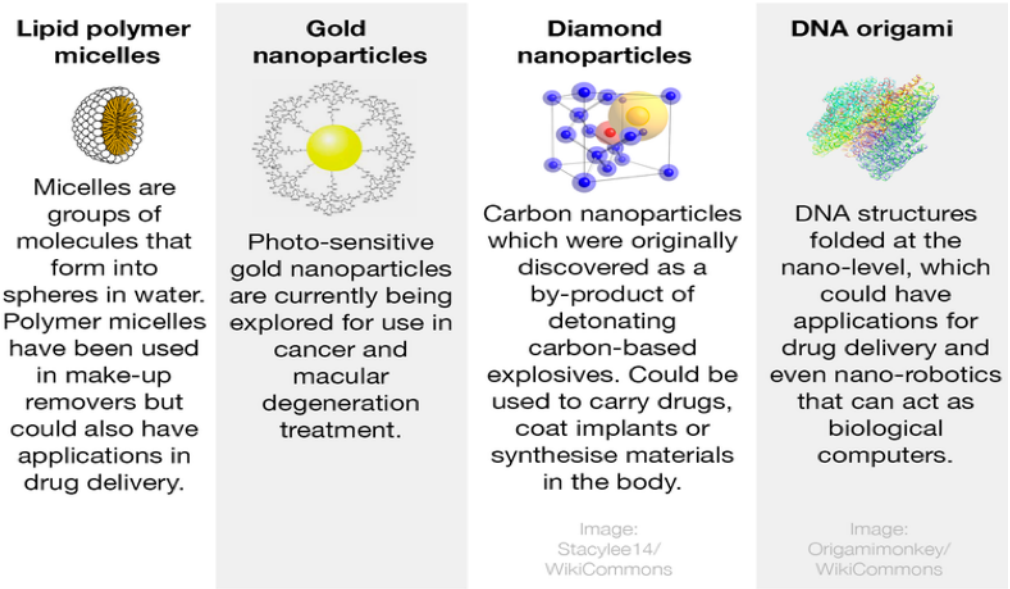
Such technologies have interesting applications in medicine, as described below in Figure 4.

Medical 'Things' and the Internet of Things

The internet of medical things (IoMT) is a healthcare application of IoT technologies and envisions a network of connected devices that sense vital data in real time. The burgeoning of IoMT has been enabled by the development of wireless sensor-based systems, nanotechnology and miniaturization. It is now possible to join the dots between personal digital devices, connected medical devices, implants and other sensors so that sensors collect data, micro-controllers process and analyse and wirelessly communicate data, and microprocessors enable rich graphical user interface.

IoMT now has an established role in a broad range of healthcare applications to support clinical decisions, reduce incorrect diagnosis, improve quality of services through the management of chronic diseases and monitoring of hospitalized patients. Some examples of applications of IoMT are highlighted in Table 8.

Figure 3: Applications of nanotechnologies in medicine



Source: The conversation. Explainer: what is nanomedicine and how can it improve childhood cancer treatment?
https://theconversation.com/explainer-what-is-nanomedicine-and-how-can-it-improve-childhood-cancer-treatment-69897

Table 8: Internet-of-things applications in health and healthcare

Telemedicine

Telemedicine refers to the process through which clinical healthcare services are provided to individuals from a distance using telecommunications and information technology. While early days telemedicine targeted patients located in remote areas or regions with a shortage of medical care providers, it has evolved to reduce time waste in doctors' waiting rooms and provide immediate care for minor but urgent conditions. Driving the rise of telemedicine are innovations in mobile medical and non-medical devices that enable patients to collect medical data and communicate them to their providers over telecommunications lines. These include devices that can take vitals, measure blood pressure, monitor glucose levels, and even test for several conditions from small blood samples; and send the results in real time to professional medical providers.

Virtual home assistants

Many senior individuals living alone require daily assistance. Unfortunately, family or paid care providers might not always be available. Virtual home assistants can help fill this void. Many technologies now allow elderly people living alone to stay connected with their family through voice and video. These assistants can help with medication adherence, by reminding their users to take their medication, and care coordination, by providing a constant link with remote care providers or family members. Seniors appreciate the sense of autonomy these assistants provide at a considerable low cost.

Medical adherence tracking

In November 2017, the FDA approved for the first time a drug with a digital ingestion tracking system. This product by Otsuka Pharmaceutical and Proteus Digital Health, called Abilify MyCite (aripiprazole tablets with sensor), has an ingestible sensor embedded in the pill which records that the medication was taken. The product is approved for the treatment of schizophrenia, acute treatment of manic and mixed episodes associated with bipolar I disorder and for use as an add-on treatment for depression in adults. The system works by sending a message from the pill's sensor to a wearable patch, which transmits the information to a mobile application so that patients can track the ingestion of the medication on their smartphone. Patients can also permit their caregivers and physician to access the information through a web-based portal.

Emergency response systems

Many innovations now seek to consistently monitor the behaviour of their users and intervene in case of emergency. These innovations offer services that include detection of falls, emergency assistance and navigation guidance back to residence or even boundary perimeter breach alerts (for patients suffering from Alzheimer's or dementia, for example), together with communication systems that alert care providers or family members in case of an emergency.

Analytics and Computing for Improved Diagnostics, Payments and Information Sharing

Artificial Intelligence

In artificial intelligence (AI), machines are programmed to develop cognitive functions for learning and problem solving. AI has the potential to augment human intelligence just as machines increased physical capabilities a century ago. Since 2010, major success in deep learning – a subfield of machine learning concerned with algorithms and inspired by the structure and function of the brain – has been achieved. This coupled with the increasing availability of health and healthcare-related data is significantly improving the impact of AI on health.

One of the key areas where AI is making a difference is in supporting diagnostics. Misdiagnosis is a concerning issue in medicine, with studies revealing that at least one adult patient in 20 is misdiagnosed every year in the US, with half of these errors being potentially harmful.[54]

AI-based methods have already shown strong results in image-based diagnosis. Recent studies are now demonstrating the potential for AI-based technology to assist physicians in diagnosing diseases. A group of researchers in the United States and China recently reported that they had built a system that automatically diagnosed common childhood diseases with high accuracy – providing proof of concept for implementing an AI-based system to aid physicians in tackling large amounts of data, augmenting diagnostic evaluations, and providing clinical decision support in cases of diagnostic uncertainty or complexity.[55]

Through its ability to sift through large amounts of information, AI also offers interesting possibilities in improving business processes related to healthcare, including, but not limited to, organizing and managing medical records and data, identifying and addressing business workflows inefficiencies and cutting billing errors. Additionally, AI can help professionals with complex decision making, such as the kind that occurs in oncologists' offices, and point out clinical nuances that health professionals might have missed. Table 9 highlights a few applications of AI to health and healthcare.

The key challenge in applying AI to healthcare is being able to translate technical success into meaningful clinical impact. There also exists ethical and legal challenges in data sharing and management, and unaddressed concerns regarding interoperability of systems, data ownership in case of partnership ventures, and legal responsibility when errors occur using these systems. The last section of this report discusses these challenges in more details.

Table 9: Artificial intelligence applications to health and healthcare[56]

Detecting skin cancer Melanoma, a cancer that forms in the melanocytes (the skin cells that produce melanin), is not easily identifiable by untrained eyes. The extent to which a doctor can confidently recognize melanoma depends on experience and training. AI can now diagnose skin cancer more accurately than experts. A recent study published in the *Annals of Oncology* showed AI was able to diagnose cancer more accurately than 58 skin experts. The AI had been trained using images of skin cancer and the corresponding diagnoses. Human doctors got 87% of the diagnosis correct, while their machine counterpart achieved a 95% detection rate.[57] Such studies are demonstrating the positive impact on diagnostic performance that AI could provide to dermatologists, ultimately improving outcomes for patients.
Eye health Our eyes are the windows to our soul, so the saying goes, but they're also a window on our health. Picking up eye problems early can significantly reduce the chance of sight loss. Several programmes are looking at how to combine existing medical knowledge about our eyes with AI tools. Google DeepMind has teamed up with Moorfields Eye Hospital in London to work on diagnosing two major conditions that cause sight loss: diabetic retinopathy and age-related macular degeneration (AMD).[58] Together, these diseases affect more than 625,000 people in the UK and over 100 million people worldwide.

Algorithms have been trained using thousands of eye scans, then set to work detecting potential issues, allowing doctors to recommend the right course of action in a fraction of the time it would normally take and with a greater degree of certainty. DeepMind says that 300,000 UK patients a year could be helped if the system is given the go-ahead for general use after the completion of clinical trials.

Drug development

AI can scan through data at a rapid rate that is impossible for humans to match. One of the ways this data crunching could revolutionize healthcare is in the development of new drugs.

The technology can analyse data drawn from a wide variety of sources, such as clinical trials, patient health records and genetic records, and help predict how a drug might affect a person's cells and tissues, leading to better trials and paving the way for a personalization of their medicine. This more streamlined process could bring drugs to market much faster.

Knowing when someone in a coma will awaken

When doctors are trying to decipher how much a patient's brain has been damaged by trauma, they use a coma scale. After performing a series of tests, the doctors give the patient a score. That score reflects the patient's prognosis and may play a part in decisions regarding the use and possible withdrawal of life-support machines.

In a Chinese trial, an AI system trained on brain scans came up with its own score, which was very different from that given by the doctors. One patient was given a seven out of 23 score by doctors, but after the technology analysed his brain scans, the AI gave him 20 . A score of seven indicates such a low likelihood of recovery that the patient's next of kin would be given the option of withdrawing life support. But true to the AI's prediction, the patient eventually woke up.

The AI got nearly 90% of cases right by tracing brain activity invisible to the human eye, such as small changes in blood flow to the brain. The system is now an integral part of the hospital's daily processes and has helped give the correct diagnosis in more than 300 people.[59]

Recognize depression

California-based MindStrong[60] has recently published a paper showing that its technology could pick up signs of depression and other mental disorders by analysing how people use their smartphones. Its proprietary technology analyses how people type – their taps, scrolls and clicks – to predict a range of cognitive traits and mood states.

AI is also showing promising signs in being able to alleviate the symptoms of depression. A recent trial involving Woebot, a chatbot that has been designed according to the principles of cognitive behavioural therapy, showed that it was effective in treating the disorder.[61] In the trial, 70 participants between 18 and 28 years old received either two weeks (up to 20 sessions) with Woebot, or were directed to the National Institute of Mental Health ebook. For those in the Woebot group, the depression symptoms reduced significantly over the study period.

Robot doctors

Doctors spend years in training, learning all about the human body and the vast number of illnesses and diseases that can befall it. They also need to keep track of up-to-date research published in medical journals and medicine development. Researchers in China showed how a robot could help doctors retrieve this information, by remembering it all for them.

In their test, the AI robot – which had absorbed the contents of dozens of medical textbooks, 2 million medical records and 400,000 articles – passed the medical licence exam test in a fraction of the time of its human peers, and with better accuracy. The robot, called the iFlyTek Smart Doctor Assistant, achieved a score of 456, significantly higher than the mark of 360 required to pass the exam.[62]

Big Data

Big data refers to very large volumes of data that are too complex for traditional data-processing tools. In the health and healthcare sector, an increasing volume of data from within and outside traditional healthcare settings has the potential to contribute to decision-making.

There are many sources of such data, in addition to medical and health records, which were the traditional sources of data in healthcare. The genetic revolution described earlier in this report has given rise to increasingly large genomic and pharmacogenomic datasets. Furthermore, sensing wearable devices, user-generated data (from web searches or social media posts, for example), or personal data (such as mobile phone use or credit card transactions) are sources of information, which, when triangulated with more traditional sources can provide powerful analytical and predictive capabilities for healthcare providers and policy-makers.

The use of big data in health has the potential to improve decision-making and address inefficiencies in the healthcare ecosystem. The case study below explains how big data could be leveraged to develop evidence-based models for precision care and payment.

Unfortunately, because of the size, speed of accumulation, complexity and heterogeneity of this data, there are difficulties in tapping them with existing tools and systems. Furthermore, the rise of big data also raises challenges in privacy, security, data ownership, data stewardship and governance, as described in the later sections of this report.

Case Study: Big Data for Rational Care[63]

The cost of healthcare in the US represents over 18% of GDP, with an estimated third ($1 trillion a year) being wasted. This pattern will continue to worsen partly due to an ageing population and rising cost of novel therapies. These mounting challenges translate into market dynamics that put pressure on the entire ecosystem, providers, payers and life science companies to improve outcomes and patients' experience while reducing costs. To answer such mounting challenges, there has been a push for alternate payments models, away from fee-for service and towards value-based care.

Pushing Towards Solutions: Value-based Care and Alternate Payments Models (APM)

Professional organizations have been engaged in efforts to streamline decisions of care. In oncology, it is the National Comprehensive Cancer Network (NCCN) that collects all recognized treatments to manage cancer patients. To address the speed of growth in acceptable options over time, NCCN developed the Evidence Blocks based on expert feedback regarding efficacy, safety, quality, consistency of data and affordability for each regimen. The goal is to help oncologists in decision-making for best value by choosing among "preferred regimens" and "other regimens". The America Society of Clinical Oncology (ASCO) developed the ASCO value framework, which offers a scoring system based on clinical benefit and toxicity and referred to as the Net Health Benefit (NHB) score, which can be compared with costs and help physicians and patients' decisions alike.[64]

A New Digital Classification to Track Individual Patients

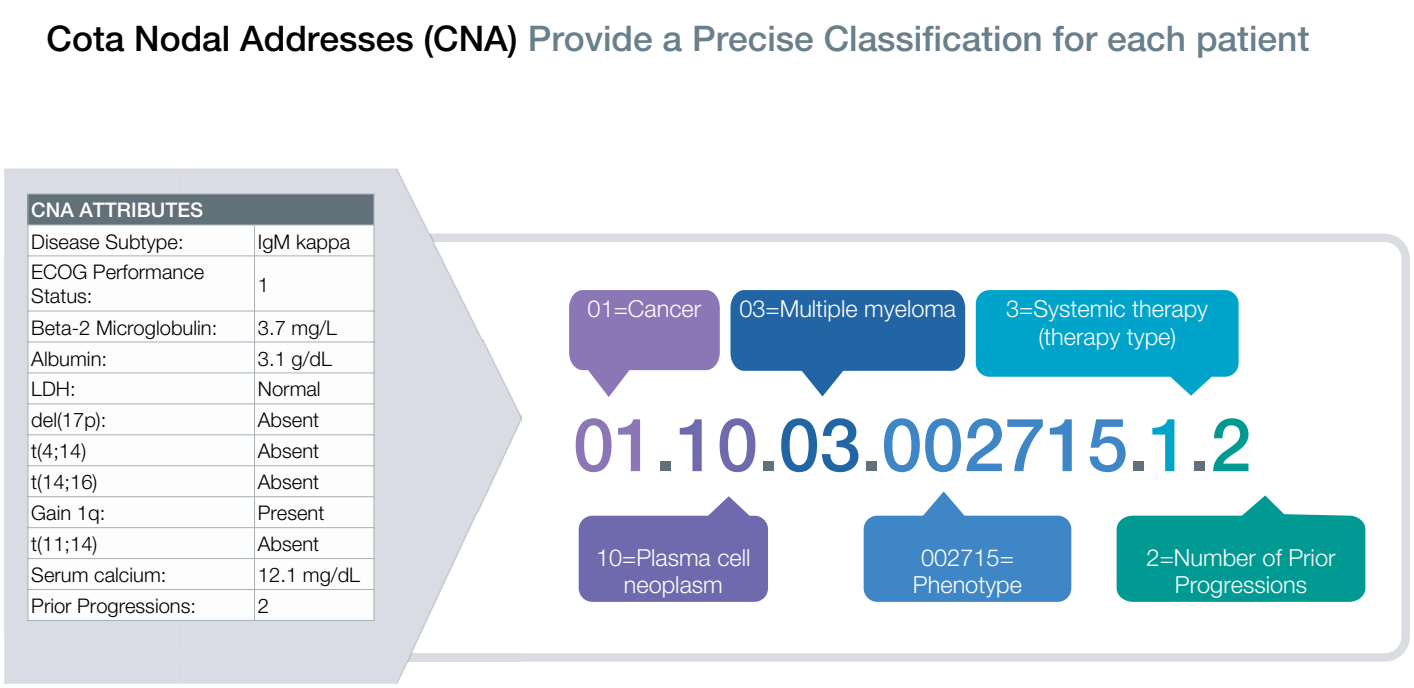
The John Theurer Cancer Center developed a new digital classification, the COTA Nodal Address (CNA), which integrates all relevant variables to make a clinical recommendation for a given patient. This model compresses all relevant data in the patient record into a digital code allowing for a precise classification of each patient not found in current standard classification systems. The information captured allows for the collection of all prognostically relevant data points along the patient journey for the entire care and follow-up until death, or long-term follow-up if the patient is cured. This information is de-identified and therefore exempt from the need for patient-informed consent and may be used for "secondary" research purposes in aggregate.

In addition, COTA captures co-morbidities, treatment dose intensity delivered for each drug, toxicities, response, progression-free survival and/or time to next therapy, overall survival, quality of life and cost. This provides a unique longitudinal visualization tool for each patient, which allows for reliable comparisons in outcome and treatment patterns. As expected – but for the first time in a proven and measurable way – CNA architecture revealed great variance in treatment recommendations and costs even within similar CNA-defined subsets of patient.

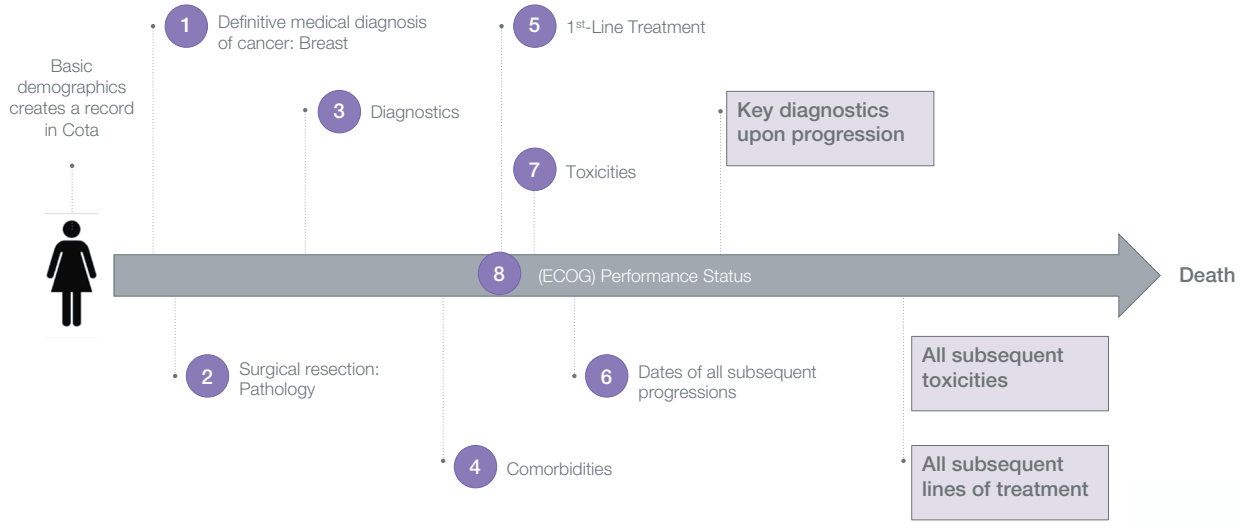
Understanding the variances in treatments and costs within groups of CNA identical patients allows strategies to optimize care and value. For example, within a series of 3,000 breast cancers treated in large practices in the New York tri-state area, significant variance in cost were identified, sometimes within the same sub-lane, due to differences in utilization of imaging and/or growth factors, while treatment recommendations differed significantly based on patients' volumes seen at each facility or by provider.

Having the ability to analyse patient data together with financial information allows care providers, after determining a list of optimal treatments for each group of patients, to eliminate higher cost options *without compromising outcomes*.

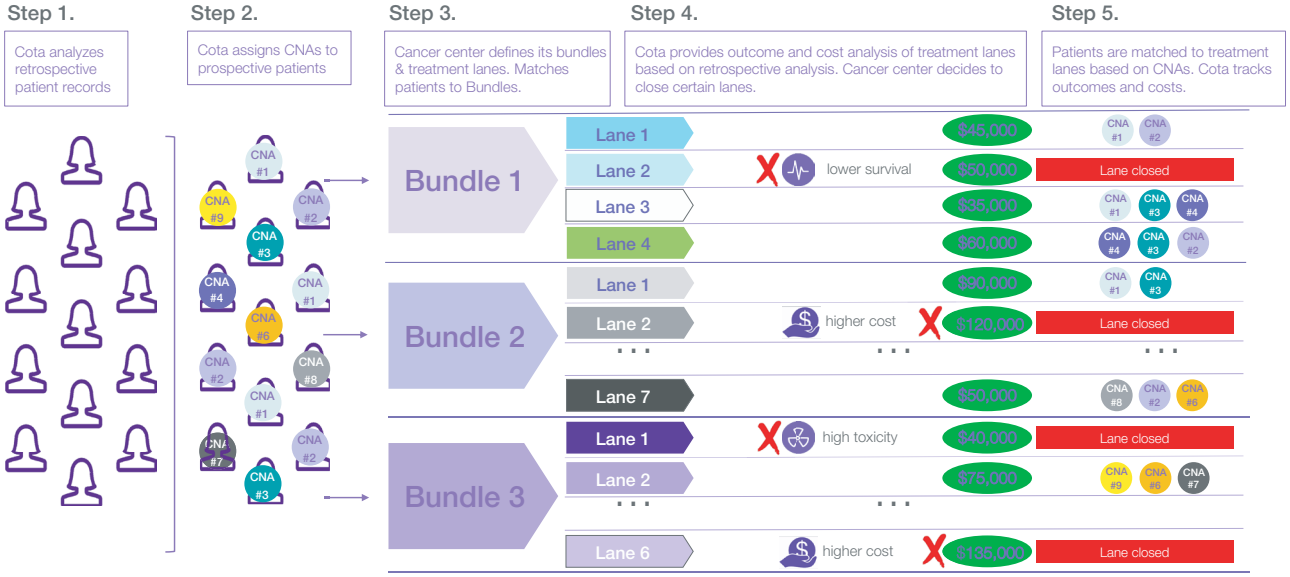
Figure 4: Developing a model for rational care based on individual patient outcome tracking and treatment decisions



Cota Collects All Prognostically Relevant Data Points Along The Patient Journey: Breast Cancer Example



How a CNA Powered Bundles Program Works: Improved Outcomes Through Adverse Variance Detection & Cost Analysis



Blockchain

Blockchain is defined as a distributed, decentralized data ledger but can be simply described as a shared database. The technology enables the creation of digital records and their sharing and management securely on a network. Each participant has an identical copy of the database, which is updated as changes are made in real time.

Blockchain is known best for its use in cryptocurrencies. Applying the technology to healthcare is compelling for three reasons: (1) its ability to create digital identities; (2) its capacity to track physical objects; and (3) its capability to support data exchange while safeguarding security, integrity, provenance, transparency and control of the data by its owner.

Owing to its ability to create digital records, blockchain has the potential to revolutionize the handling and sharing of medical records. Its ability to record digital events, enable peer-to-peer sharing between parties, and ability to exchange complex health data/information between patients, providers, payers and other sources (employee wellness programmes, wearable health monitors, etc.) could potentially overcome interoperability challenges in current health IT systems.

Blockchain could have an important role in claims adjudication and billing management. By eliminating the need for intermediaries, blockchain could reduce administrative costs. A blockchain-enabled healthcare claims management solution could potentially prevent fraud and minimize losses. Medical billing related frauds have been estimated to amount to 3%-10% of total healthcare spending in the US.[65]

Through its ability to track physical objects, Blockchain can also enable drug supply chain integrity and provenance management by maintaining a chain of custody log. This would yield significant benefits: sales of counterfeit medication are estimated to range between $163 billion to $217 billion a year,[66] with up to 30% of pharmaceuticals estimated to be counterfeit in some markets.[67]

Blockchain also has an application in ingraining integrity in the reporting of clinical trials and population's health research. Studies show that roughly 30%-50% of clinical trials go unpublished, and that those trials that are published tend to be those with favourable results, a bias which is suspected to distort medical evidence.[68]

While blockchain can be transformational to address many healthcare system challenges, there are many caveats in its use, which necessitate building appropriate safeguards. Standards and ethics in relation to governance of blockchain networks, and roles, responsibilities and accountabilities of data-centric security companies, need to be carefully defined. Privacy and data-protection should be safeguarded. Moreover, as the volume of data raises storage issues, new mechanisms of data storage such as data-lakes or off-chain data storage need to be advanced.

Virtual/Augmented Reality

Virtual reality (VR) is an artificial, computer-generated simulation or recreation of a real-life environment or situation. Augmented reality (AR) is a technology that layers computer-generated enhancements on top of an existing reality to make it more meaningful through the ability to interact with it. Both have great potential in changing the medical landscape.

Virtual and augmented reality technologies have recently been leveraged to contribute to treatment protocols for mental health conditions. This is because VR technologies offer greater access to interventions by enabling direct active learning and coaching in real-world situations, without therapists having to make time for sessions outside the clinic. Applications of VR for the treatment of mental health conditions are currently tested against psychological conditions such as post-traumatic stress disorder (PTSD)[69] and phobias.[70]

Other applications are being explored at nascent companies looking to leverage AR or VR in healthcare applications. Promising work includes turning wearable technology into neuro-assistive devices for people on the autism spectrum,[71] vein-visualization devices to improve the success rate of intravenous access in healthcare settings,[72] and using AR technology to teach anatomy to medical students[73] or bring outside information into a doctor's field of vision.[74]

Modern Machines and Healthcare

3D Printing

3D printing is an additive manufacturing process, in which a three-dimensional physical object is created from a digital design by printing material layer by layer. After an additive manufacturing patent expired in 2009, its use has grown exponentially. The medical and prosthetics field has largely benefited from the adoption of 3D printing with the manufacturing of assistive medical devices, braces and retainers that can be tailored specifically for the needs of their end-user.

Recent advances in 3D printing are opening further options in medicine. One notable case is that of 3D printing for pharmaceutical production. The technology allows for the tailoring of drug dosage, size, form or release profile to the need of users with unique challenges (such as children, for example, who may need smaller doses, or may more readily agree to swallow a pill that has a pleasing colour and is in the shape of an animal). 3D design and printing may also allow for the combination of multiple drugs into one pill; an interesting advantage for patients who take multiple medications daily.[75] This revolution in drug manufacturing is already a reality: in 2015, the FDA approved an epilepsy medicine called Spritam,[76] the first 3D-printed product approved for use inside the human body in the US.

3D printing for medical or pharmaceutical products, although exciting because of the avenues it offers in democratizing and tailoring medical products and therapies to the unique needs of patients, also presents significant regulatory challenges to ensure the quality of 3D-printed products.

Robotics

Robots have been used to improve surgical precision for many years. The da Vinci Surgical System,[77] for example, has enabled surgeons to operate with enhanced vision, precision and control for years. The company claims to have brought minimally invasive surgery to more than 3 million patients worldwide.[78]

Work in most recent years is looking to bring together robotic interfacing with digital technology, AI, VR and AR to address key healthcare challenges. Robots are also becoming an attractive technology in thinking about caring for an increasingly elderly population. These applications should not be intended to replace human healthcare providers but to free their time from cumbersome tasks leaving more resources to spend on issues requiring human decision-making and interaction.

Drones

Unmanned aerial vehicles are on the rise.[79] Amazon expanded the use of drones beyond aerial photography and initiated delivery of goods through drones in 2016,[80] but efforts were thwarted by regulatory, safety and privacy issues and concerns that drones may be used for illicit purposes, such as smuggling weapons or drugs into prisons or across borders.

Drones have great potential in making the transport of drugs, vaccines or medical aids faster, especially during disasters or medical emergencies. In responding to and recovering from the 2010 Haitian earthquake, and the 2013 typhoon Haiyan, drones were used to assess damage and support the allocation of resources.[81,82]

These approaches were also tested in the US to understand how drones could be used in disaster settings.[83] Drones could be useful in transporting blood products, expensive and rarely used drugs and perishable items to remote hospitals, mass casualty scenes and even offshore ships with seriously injured passengers, especially in situations where safety, accuracy and speed are important.[84]

Medicine-carrying drones have now been tested or used in Madagascar,[85] Papua New Guinea,[86] Bhutan,[87] Malawi[88] and Tanzania.[89] The most well-documented example of drone use in healthcare is in Rwanda, where the government has teamed up with a company to deliver medical supplies to five of its hospitals through medical drones.[90,91]

Table 10: Applications of drones in health and healthcare

– Ambulance drones are being used in the Netherlands and have inspired the delivery of automatic external defibrillators directly to people who have just suffered a heart attack.[92]
– Google has recently patented a device that can call for a drone in an emergency to fly in with life-saving medical equipment onboard.[93]
– A system for drones that can deliver blood and heart or other organ transplants to isolated parts of Australia is also being developed.[94]

Policy and Governance: Adjusting Our Society to Rapid Changes in the Health and Healthcare Ecosystem

New innovations and technologies will accelerate the pace of change and create new opportunities, but they may also aggravate existing divisions and disparities. Advances in data and automation pose the risk of displacing workers. Biotechnologies such as genome editing will revolutionize health and medicine, yet also raise many ethical, legal and societal challenges.

Access and Affordability

Access and affordability are key considerations as we think about the implementation and governance of emerging technologies. The new technologies must be available to everyone. There are serious concerns that innovations will increase healthcare spending. Expensive innovations have been cited as a key cause of rising healthcare costs in the US, which already spends 17% of GDP or nearly $3 trillion on healthcare.[95] According to the November 2013 issue of the *Journal of the American Medical Association* (JAMA), an increase in the price of drugs, medical devices and hospital care accounted for 91% of the rise of healthcare costs between 2000 and 2011. This trend is unacceptable and unsustainable.

However, some innovations may be cost-saving in the long term despite high initial costs. For instance, a recent analysis based on short-term data found that two new CAR-T cancer therapies, Kymriah (Novartis) and Yescarta (Gilead), which have a one-time cost of $475,000 and $373,000, respectively, are cost-effective relative to standard chemotherapy treatment.[96] Clearly more work is needed in this area. Novel therapies must address their cost-effectiveness as well as long-term economic impact.

Pricing and payment models must reflect the expected impact of new technologies on health outcomes and be responsive to ongoing evidence of actual impact.

Workforce

It will be impossible to successfully implement and adopt these costs without an effective workforce – one with the right skills and composition of professions to support the new directions of health and healthcare.

New advances and technologies have important workforce implications. It is important to recognize that the nature of the workforce of the future will be different from the workforce of today. Some professions/sectors may be negatively affected if certain considerations are not taken into account. Notably, some jobs will disappear while others will be transformed.

For instance, as AI advances, tasks such as radiologic image and tissue pathologic interpretation could be performed more efficiently and accurately by computers. **It is clear that policy-makers and other stakeholders, such as professional societies, will need to think about the implications for education and training. In other words, how education will need to evolve for those entering the workforce as well as how to retrain the existing workforce to align with evolving technologies and labour trends.**

Regulation

Regulation will be important to ensure that patients are not harmed by emerging technologies – especially those that enter the market before there is enough evidence (whether this is done in a legal manner or not) to ensure this is the case. For example, the FDA has taken steps recently to rein in the unregulated stem cell industry.[97] However, existing regulatory systems are often ill-equipped to oversee emerging technologies.

Our existing regulatory frameworks will need to be examined to ensure they are suitable for emerging technologies. We will need to rethink the way evidence is collected and evaluated. An emerging approach is for healthcare organizations to collect data as part of ongoing clinical care to generate data on patient and economic outcomes. Although further research is needed to validate this model, it holds promise as an approach to address the surge in development of new therapies, the increasing cost of randomized controlled trials, and the escalating need to collect data to support regulatory approval for coverage decisions. As this approach continues to gain traction, the question becomes when should randomized controlled trials be required?

Decision makers must modernize governance frameworks and implement policy levers in order to encourage appropriate use of health technologies, balancing the need to protect patients, spend resources wisely, and continue to promote future innovation.

Ethics, Equity and Social Considerations

New advances on the horizon raise a number of social and ethical considerations. Of particular importance is how to ensure that the distribution of risks and benefits of new advances is fair and equitable. Certain technologies will have important implications for societal structures (e.g., families), belief systems (e.g., religion) and cultural norms (e.g., attitudes about sexuality, race, disability). For example, the potential to use genome-editing technology

for enhancement raises concerns about creating pressure for individuals, especially those with disabilities, to use technologies they would not otherwise choose. The effects of such a scenario may ultimately extend to public policy – it is not hard to imagine that a reduction in the frequency of birth defects may lead to weaker public support for accommodating the needs of people with disabilities.

As policymakers work to enact new governance frameworks, attention to potential social and ethical concerns is paramount. Dialogue and engagement with patients and the public must also be embedded into efforts to develop new governance frameworks.

Norms, Standards, Responsible Conduct

The rapid advances in science and technology are accelerating the need for ethical norms and standards to govern behaviour. It is important that the scientific community engage different stakeholders, including the public and social, ethical and religious groups to develop norms and standards for conduct that distinguish between acceptable and unacceptable behaviour. Furthermore, different societies will need to consider the implications of new advances in the context of their diverse historical, cultural and social characteristics – thus, specific regulatory or legal frameworks will differ from country to country.

Nevertheless, policymakers should consider ethical principles for emerging technologies, such as those outlined for human genome editing by the National Academies (2017), as they develop their own governance frameworks.

Data Ownership, Privacy and Sharing

Patient data is central to many of these advances; however, questions about data ownership, privacy and sharing remain. Patients have a right to own their data and control how it is used. Regulatory systems and other protocols must be in place to protect patients' rights regarding their data and to ensure that patients feel comfortable sharing their personal health information.

Furthermore, as big data and analytics and AI become more pervasive in healthcare, we need to guard against bias. There is a widespread belief that software and algorithms that rely on data are objective. But software is not free of human influence. Algorithms are written and maintained by people, and machine-learning algorithms adjust what they do based on people's behaviour. As a result, researchers in computer science, ethics and law have noted that algorithms can reinforce human prejudices.

For example, several states in the US have begun to use an algorithm to predict the risk of re-offence and this risk score is used in part to determine sentencing. Although race or ethnicity are not explicitly identified as variables, the algorithm has been shown to be biased against African Americans. An investigation by ProPublica indicated that the algorithm is more than twice as likely to falsely flag black defendants as future criminals compared with white defendants.[98]

Policy makers must work together with other stakeholders, including industry, and academia to ensure that AI does not promote inequity. Governance frameworks and policy levers that promote transparency concerning the use of data and AI, maintain mechanisms for human oversight of AI, and encourage the development of incentives around data and AI that align with the public good are only a few necessary solutions.

Biosecurity and Biosafety

New biotechnologies and scientific advances offer incredible promise but also raise concerns for "dual-use" (unintentional misuse or deliberate malicious use of research). Notably, the US Director of National Intelligence James R. Clapper sent shockwaves through the national security and biotechnology communities with his assertion, in his Worldwide Threat Assessment testimony to the Senate Armed Services Committee in February 2016, that genome editing had become a global danger. Clapper noted that the new technology could open the door to "potentially harmful biological agents or products," with "far-reaching economic and national security implications."[99] Similarly, the World Economic Forum described a "transformation of biological risk" in *The Global Risks Report 2019*.[100]

While emerging technologies make it increasingly easy for new biological threats to be manufactured and released – either deliberately or by accident – the possible gains are profound, not only to healthcare but also in areas of chemicals, fuels, electronics and others. Realizing these benefits will require managing risks, including by implementing rigorous transparency and oversight requirements, as well as relying on stronger norms for work that might increase risks.

Cybersecurity

As the collection and exchange of personal data become even more ubiquitous, it will be increasingly important to ensure that personal information is protected and secure. In 2016, healthcare was the fifth most targeted industry when it came to cyberattacks. More than 16 million patient records were stolen from healthcare organizations in the US and related parties that year.[101] In the coming years, this threat is only likely to increase, with cyberattacks becoming increasingly sophisticated.

Hospitals and health systems are vulnerable to cyberattacks that could put patients in danger. These issues range from malware that compromises the integrity of systems and privacy of patients to distributed denial of service (DDoS) attacks that disrupt facilities' ability to provide patient care. Furthermore, attacks to broader infrastructure, such as the electric grid, could stop hospitals from functioning. Any medical device connected to a network is potentially at risk from being taken over and exploited by hackers, from MRI machines to electric wheelchairs. Health systems as well as individuals will need to become more aware of their vulnerability to cyberattacks and start to take measures to protect themselves.

Policy makers can promote such efforts by enacting policies and more stringent requirements around privacy and data security.

Conclusion

The rapid pace of advances in science and technology in the Fourth Industrial Revolution has important implications for health and medicine. Advances in fields such as genetics, genetic engineering, precision medicine, data science, and more are giving rise to new diagnostic and therapeutic modalities which offer the possibility of curing disease, reducing suffering, lengthening lives, and more. Yet, these breakthroughs also come with unintended and (often) unforeseen consequences, with potentially important societal impact. Will emerging therapies only be available to a select portion of society? Will costly new therapies exacerbate existing health disparities? Will new technologies, such as CRISPR-Cas9, be used for enhancement purposes? Will health care professionals be prepared to appropriately deploy new technologies in clinical care? Will technology disrupt the doctor-patient relationship? Will patient data be adequately protected? These are only a few of the many questions that will have to be addressed for emerging technologies to have positive impact on health and society.

The advances of science and technology are out-pacing existing care and payment models, regulatory structures, and other governance systems. Thus the Fourth Industrial Revolution's effects on the future of health and human well-being, and the implications on society need to be elevated and collectively examined in the public discourse. Currently, the effects of certain advances remain largely undefined and unaddressed while many conversations have taken place in a somewhat siloed fashion. There is a need to educate the public, policy makers, and providers about the impending transformation, modernize existing governance systems and structures, and develop a coordinated and collective framework.

The 2016-2018 Global Future Council on the Future of Health and Healthcare prepared this report to illustrate the transformative potential of this revolution in health and healthcare through concrete examples of emerging scientific advances and biotechnologies. This report is intended to serve as a starting point for further dialogue of how emerging technologies can be implemented and deployed in order to improve individual and population health and maximize human welfare while addressing the attendant risks to society.

It is the hope of the council to stimulate collaboration between policy-makers, innovators, practitioners, and the public to anticipate and prepare health systems and society for this revolution.

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Lead authors

Andre Goy, Council Co-Chair; Chairman and Executive Director; Chief of Lymphoma John Theurer Cancer Centre
Sania Nishtar, Council Co-Chair, Founder and President, Heartfile
Victor Dzau, President, US National Academy of Medicine
Celynne Balatbat, Special Assistant to the President, National Academy of Medicine, USA
Rihana Diabo, Project Specialist, Research and Analysis, Shaping the Future of Health and Healthcare, World Economic Forum

Reviewers

Ryan Morhard, Lead, Global Health Security, World Economic Forum
Gary Phillips, Council Member; President and Chief Executive Officer, Orphamed, Inc.
Elissa Prichep, Project Lead Precision Medicine, World Economic Forum Centre for the Fourth Industrial Revolution
Gabriel Seidman, Project Leader, Boston Consulting Group; Project Collaborator, Value in Healthcare, World Economic Forum

Council members

Andre Goy, Council Co-Chair, Chairman and Executive Director; Chief of Lymphoma John Theurer Cancer Centre
Sania Nishtar, Council Co-Chair, Founder and President, Heartfile
Nerio Alessandri, Founder and Chairman, Technogym SpA
Mark Britnell, Global Chairman, Healthcare KPMG
Fiona Bull, Program Manager, NCD Prevention, World Health Organization
I-han Chou, Senior Editor and Editorial Head, Nature
Sally Davies, Chief Medical Officer, United Kingdom
Victor Dzau, President, National Academy of Medicine, USA
Deborah DiSanzo, General Manager, IBM Watson Health
Mazen S. Darwazeh, Vice-Chairman and Chief Executive Officer MENA, Hikma Pharmaceuticals Plc
Paul Hogan, Founder and Chairman, Home Instead Inc.
Jen Hyatt, Founder Troo Life Coach
Na'am Jamshed, Senior Director, Government Affairs and Policy Middle East, Johnson & Johnson
Khaliya, Founder, Falkora
Birgit König, Chief Executive Officer, Health Germany, Member of the Board, Allianz
Bente Mikkelsen, Head, Secretariat, WHO Global Coordination Mechanism, World Health Organization
Tolu Oni, Associate Professor, University of Cape Town
Andrey Zarur, Managing General Partner, Kodiak Venture Partners
Gianluca Pettiti, Thermo Fisher Scientific (China) Inc.
Gary Phillips, President and Chief Executive Officer, Orphamed, Inc.
Peter Piot, Director and Professor of Global Health, London School of Hygiene and Tropical Medicine
Qian Xu, Professor and Chairwoman, Department of Maternal and Child Health, Fudan University
Johanna Ralston Lamb, Chief Executive Officer, World Obesity Foundation
Naveen Rao, Lead, MSD for Mothers
Bright Simons, President, MPedigree
Vivian Tan, Vice-President, Strategy and Transformation, Kaiser Permanente
Humain Mohammed Obaid Al Qutami, Director-General, Dubai Health Authority

Council manager

Emmanuel Akpakwu, Former Project Lead, Global Health and Healthcare, World Economic Forum

Forum Lead

Vanessa Candeias, Head, Shaping the Future of Health and Healthcare, Member of the Executive Committee, World Economic Forum

Endnotes

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World Economic Forum
91–93 route de la Capite
CH-1223 Cologny/Geneva
Switzerland

Tel.: +41 (0) 22 869 1212
Fax: +41 (0) 22 786 2744

contact@weforum.org
www.weforum.org