

# Four Decades of Innovation in Medicine (1980-2021)

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## Abstract

The field of Medicine has advanced at a very fast pace during the last 40 years thanks to the technological and digital revolution. A number of different innovations have taken place during this time period, from inventions of newer types of medicines, innovative surgical procedures, in-depth investigative methods, and advanced technological devices. In the 1980s, a number of technological innovations took place including the emergence of the first commercial MRI scanner, personal glucose meter, and cochlear implants. There were surgical advancements like laser cataract surgery, the invention of surgical robot, and the intravascular stent. There was development of newer types of medications like the invention of Human Insulin and the first commercial hepatitis B vaccine. Polymerase chain reaction (PCR) and automated DNA sequencer were invented and DNA fingerprinting was done for the first time during this decade. In the 1990s, Human Genome Project began and Dolly, the sheep became the first mammal cloned. Newer treatment modalities began like cancer immunotherapy and targeted cancer therapy. Combination drug therapy for HIV (HAART) extended HIV survival. The first human embryonic stem cell line was created and Q-switched lasers, DNA microarray, and bionic limbs were invented during this decade. The 2000s witnessed the completion of the Human Genome Project with the completion of sequencing of the human genome. The first full-face transplant and first telesurgery were also done during this time period. Capsule endoscopy got FDA approval during this decade and there was invention of HPV vaccination. In the 2010s, the first successful synthetic cell, first artificial pancreas, and the first 3D-printed heart using human cells were created. The first skull transplant was done. Bionic Eye was invented, TAVR and eTNS System were given FDA approval. The first cancer vaccine (sipuleucel-T), first Ebola vaccine, and a new drug called Sofosbuvir with a 95% cure rate for Hepatitis C were FDA approved. Checkpoint inhibitor therapy was invented and the first gene therapy and CAR-T cell therapy were given FDA approval. Genome Guided Solid Tumor Diagnosis began and the use of Artificial Intelligence initiated especially in preventative and diagnostic healthcare. During the COVID-19 pandemic, different COVID-19 vaccinations were given FDA or WHO emergency use authorization in 2020 and 2021 including Pfizer-BioNTech, Moderna, Janssen, AstraZeneca, Sinopharm, Sinovac, and COVAXIN. These innovations have opened up possibilities that were previously unimaginable in earlier decades, and have also paved the way for future advancements in medical research and delivery of healthcare.

## Key Words

Human Genome Sequencing, Cancer Immunotherapy, Stem Cell Therapy, 3D Bioprinting, Functional Magnetic Resonance Imaging, TAVR, Computer-Aided Diagnosis, Bionics, Robotic Surgery, Vaccines

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## Introduction

During the past few decades, technological development has taken place at a remarkably rapid pace and advancements have been made at a faster and greater rate than at any other time in human history. Enormous strides have been made in every realm of science and technology including healthcare and medicine. In the field of medicine, a number of life-changing and fascinating advances have taken place that would not be even in the wildest imagination of people a few decades ago bringing a revolution in the treatment and management of disease leading to improvement in the patients' quality of lives. With increased knowledge of the inner workings of the human body and technological advancements, nothing appears to be impossible. The disease has always been a source of both terror and curiosity throughout history. These advances unravel the complicated mysteries of disease and medicine and demonstrate the ability of humans to collaborate to create a brighter, healthier future for all. This article presents a glimpse of some important advances in medicine during the last four decades that revolutionized medicine and healthcare.



Fig. 1. Some Major Medical Advances During the Last Four Decades

**a.** DNA Profile **b.** Functional Magnetic Resonance Imaging (Thomas Angus/CC BY-SA 4.0) **c.** i-Limb (Danie Ware/CC BY 2.0) **d.** Personal Glucose Meter (Omstaal/CC BY-SA 4.0) **e.** Bioprinting (Philip Ezze/CC BY-SA 4.0) **f.** da Vinci Robotic Surgical System (Nimur/CC BY-SA 3.0) **g.** COVID-19 Vaccines (Agência Brasília/CC BY 2.0) **h.** Diabetic Retinopathy Laser Surgery **i.** Capsule Endoscopy (TMKO/CC BY 3.0)

## **Some Major Medical Advances During the Last Four Decades**

### **Development of DNA Sequencing Technologies and Human Genome Sequencing**

In 1985, Kary Mullis published the first paper that described the Polymerase chain reaction (PCR) that was invented by him (Saiki et al., 1985). Through a polymerase chain reaction, a small amount of DNA can be copied in large quantities over a short period of time. In this process, the DNA molecule's two strands are separated by the application of heat, and DNA building blocks are added to bond to each strand. DNA polymerase helps in the formation of new DNA chains and the process can be repeated again. DNA profiling or DNA fingerprinting is the process of determining an individual's DNA characteristics. The first patent for the use of DNA's individual differences for forensics was filed by Jeffrey Glassberg in 1983. Later, Alec Jeffreys independently developed a DNA profiling process in 1984. Alec Jeffreys used DNA fingerprinting for the first time in a disputed immigration case in 1985. The first Automated DNA sequencer (AB370A) was released in 1986. In 1994, the first DNA microarray product (GeneChip) was released (Lenoir & Giannella, 2006). DNA microarrays are used to genotype multiple regions of a genome or to measure the level of expression of large numbers of genes at a time. In 1995, Pat Brown and colleagues at Stanford University developed a way to make microarrays or gene chips in the laboratory. The first rapid-cycle PCR with real-time fluorescent monitoring and melting curve analysis (LightCycler) was launched in 1996 (Lyon & Wittwer, 2009). First Low-Cost Next Generation Gene Sequencer, Polonator G.007 with freely available software and protocols was launched in 2008. In 2015, a Desktop Genome Testing Device, Juno, "The Desktop DNA Lab" was developed.

Human Genome Project was started by National Human Genome Research Institute in 1990 to sequence the human genome. In 1998, Celera Genomics also started sequencing the human genome using a different "shotgun" sequencing technique. In 2000, the initial rough draft of the human genome was released to the public on the Internet. Human Genome Project was successfully completed in 2003 with the completion of draft sequencing of the human genome and the final draft of Human Genome was released by National Human Genome Research Institute and Celera Genomics. In 2007, Celera Genomics published updates to the genome. In 2006, George Church launched Personal Genome Project to correlate genotypes with phenotypes of individuals. National Human Genome Research Institute began Human Microbiome Project in 2008 to study the human as a supraorganism composed of non-human and human cells, with the goal of describing the human microbiome and analyzing its role in human health and disease, and to characterize the metagenome of the microbiomes of 300 healthy people, over time. In 2012 Pan-Cancer analysis project was launched by The Cancer Genome Atlas Research Network (TCGA) to assemble coherent, consistent TCGA data sets across tumor types, as well as across platforms, and then to analyze and interpret those data. A set of 24 papers analyzing whole genome sequencing and transcriptomic data from 38 tumor types was published by the International Cancer Genome Consortium and TCGA Pan-Cancer Analysis of Whole Genomes project in 2020. A catalog of the mutational signatures caused by 41 environmental agents linked to cancer was developed in 2019 (Kucab et al., 2019). In 2021, Telomere-to-Telomere Consortium assembled the first truly complete 3.055 billion base pair sequence of a human genome addressing the previously remaining 8% sequence of the genome, representing the largest improvement to the human reference genome since its initial release (Nurk et al., 2021).



Fig. 2. A PCR machine (Bio-Rad DNA Engine Peltier Thermal Cycler)



Fig. 3. A chemist reads a DNA profile

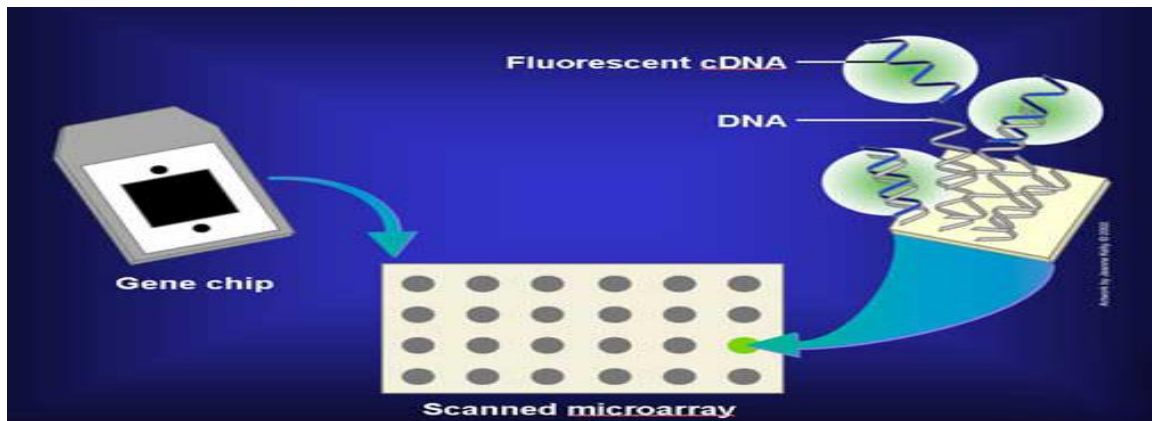


Fig. 4. DNA Microarray



Fig. 5. A Genomic DNA Sequencer (Illumina MiSeq)

### Next Generation Sequencing Based Diagnostic Tests and Targeted Therapies

The first breakthrough-designated next-generation sequencing-based in vitro diagnostic (FoundationOne CDx) was approved by FDA in 2017 to detect a number of different genetic mutations in 324 genes and two genomic signatures in any solid tumor type. The first liquid biopsy next-generation sequencing companion diagnostic test (Guardant360 CDx assay) was approved by FDA in 2020 to identify patients with specific types of mutations of the epidermal growth factor receptor gene in a deadly form of metastatic non-small cell lung cancer.

In 1998, FDA approved Trastuzumab as the first targeted therapy for HER2-positive metastatic Breast Cancer. Gene therapy of two 7-year-olds with adrenoleukodystrophy by treating bone marrow cells with a lentiviral vector carrying the gene for the enzyme they lacked apparently arrested the progress of the disease in 2009 (Cartier et al., 2009). FDA approved Vemurafenib as the first targeted therapy for late-stage melanoma that inhibits B-Raf enzyme in 2011. In 2016 first baby was born to a mother who was carrying genes for the fatal Leigh syndrome (that affects the DNA in mitochondria) using Mitochondrial replacement therapy (Zhang et al., 2017). Nusinersen, an RNA-based therapy that contains an antisense oligonucleotide that controls the mutations caused in the chromosome 5q by selectively binding and targeting RNA and regulating gene expression was approved by FDA in 2016 for spinal muscular atrophy. First in vivo directly

administered gene therapy (Voretigene neparvovec) was approved by FDA in 2017 for the treatment of biallelic RPE65 mutation-associated retinal dystrophy. A study in 2017 showed correction of the heterozygous MYBPC3 mutation (a heritable cardiomyopathy mutation) in human preimplantation embryos using CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) (Ma et al., 2017). Three targeted cancer therapy drugs were approved by FDA in 2017 for acute myeloid leukemia (midostaurin for FLT3-mutated AML, enasidenib for IDH2-mutated AML, gemtuzumab ozogamicin for CD33-positive AML). In 2018, first genetically edited babies were born. CRISPR was used to edit embryos' germline cells to disrupt the gene for CCR5, a protein on the outer surface of cells that HIV uses to enter to ensure that these babies would be protected from contracting HIV infection. In 2021, FDA approved amivantamab-vmjw as the first targeted therapy for adult patients with non-small cell lung cancer whose tumors have epidermal growth factor receptor (EGFR) exon 20 insertion mutations.

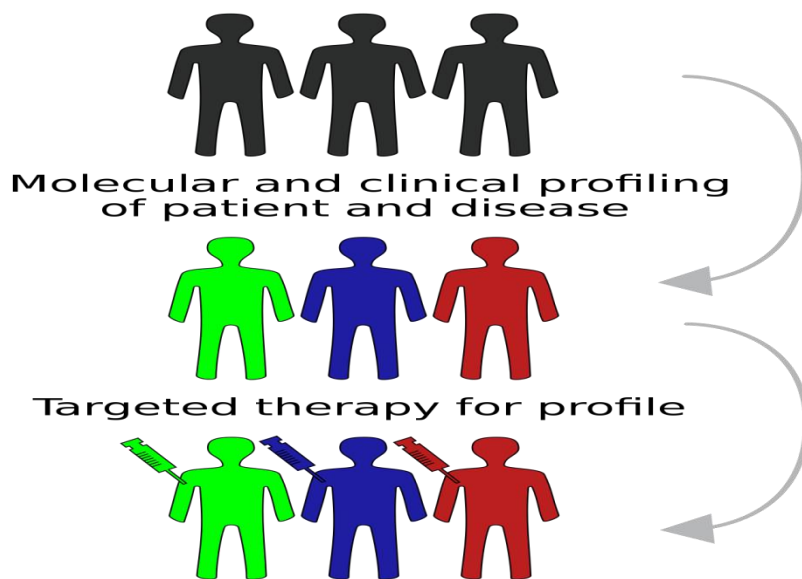


Fig. 6. Patients and their diseases are profiled in order to identify the most effective targeted therapy for their specific case (Simon Caulton/CC BY-SA 4.0)



Fig. 7. Companion diagnostic tests show which patients could be helped by a drug and which patients would not benefit leading to Personalized Medicine

## Cancer Immunotherapy

Cancer immunotherapy improves on the immune system's natural ability to fight cancer. In 1980, Sidney Pestka developed the procedure to clone interferons (Maeda et al., 1980). His work with IFN- $\alpha$  has led to cancer therapy with interferons. Monoclonal antibody therapy is a form of immunotherapy that uses monoclonal antibodies (mAb) to bind mono-specifically to certain cells or proteins to stimulate the patient's immune system. Muromonab-CD3, the first therapeutic monoclonal antibody was approved by FDA in 1986. In 1997, FDA approved Rituximab for the treatment of non-Hodgkin's lymphoma. Rituximab was the first approved monoclonal antibody for the treatment of a cancer. In 1991, FDA approved the first immunotherapeutic agent (Interleukin 2) for metastatic kidney cancer. Adoptive Cell Transfer involves taking immune cells from patients and reprogramming them with receptor molecules to target specific types of cancer. The cells are then infused back into the body. In 2006, as an advancement in Adoptive Cell Transfer, it was shown for the first time in humans that administration of normal circulating lymphocytes transduced with a retrovirus encoding a T-cell receptor that recognized the MART-1 melanoma-melanocyte antigen could mediate tumor regression. The first cancer vaccine (sipuleucel-T) was approved by FDA in 2010 for castration-resistant prostate cancer. Checkpoint inhibitor therapy is a form of cancer immunotherapy that block inhibitory checkpoints to restore immune system function. In 2011 The first Checkpoint inhibitor anticancer drug ipilimumab (a CTLA4 blocker) was approved by FDA for the treatment of melanoma. Chimeric antigen receptors (CARs) are receptor proteins that combine both antigen-binding and T-cell activating functions into a single receptor and have been engineered to give T cells the new ability to target a specific protein. CAR-T immunotherapy modifies T cells to recognize cancer cells so that cancer cells can be effectively destroyed. In 2017, the first Chimeric Antigen Receptor (CAR) T-cell therapies were approved by FDA. Tisagenlecleucel was approved for acute lymphoblastic leukemia and Axicabtagene ciloleucel was approved for Diffuse Large B-cell lymphoma.

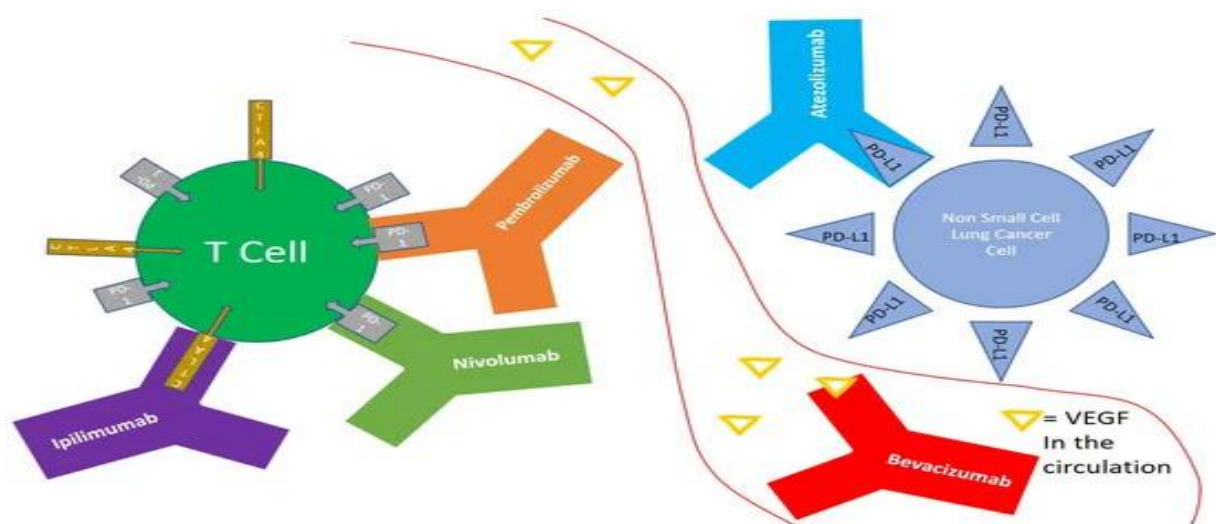


Fig. 8. Monoclonal antibodies used in the treatment of non small cell lung cancer

PDL1, PD-1 and CTLA-4 prevents autoimmunity but also prevent the immune system from killing cancer cells. VEGF stimulates the formation of blood vessels in cancer cells that provide nutrients and oxygen and cause increased growth of cancer. Atezolizumab is an anti PD-L1 monoclonal antibody. Nivolumab and Pembrolizumab are anti PD-1 monoclonal antibodies. Ipilimumab is a monoclonal antibody that targets CTLA-4. Bevacizumab is a monoclonal antibody that targets VEGF (Nasser et al, 2020/CC BY 4.0).

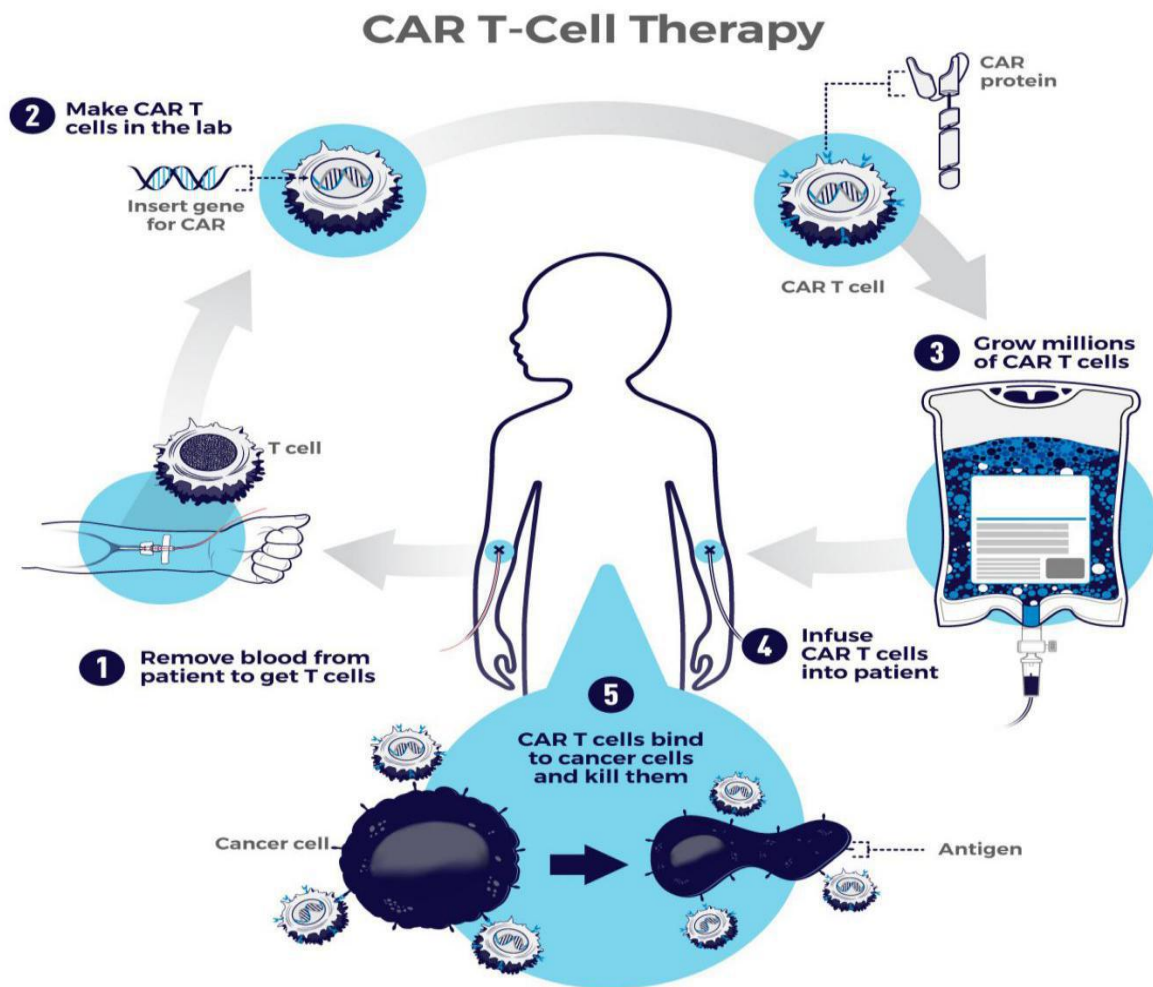


Fig. 9. CAR T-Cell Therapy

## Stem Cell Therapy

The use of stem cells to cure or prevent a disease or condition is known as stem cell therapy. Hematopoietic stem cell transplantation is currently the only established stem cell therapy in which cells are obtained from bone marrow transplantation or from umbilical cord blood. Hematopoietic stem cell transplantation pioneered by Edward Donnall Thomas and Robert Alan Good has been used to treat persons with leukemia and lymphoma for past many decades. The majority of FDA-approved stem cell-based medical products are cord blood-derived hematopoietic stem cell products for the treatment of blood and immunological diseases.

Pluripotent stem cells give rise to every other cell type in the body and represent a single source of cells that could be used to replace those lost to damage or disease. Embryonic stem cells are the most well-known type of pluripotent stem cells. James Alexander Thomson derived the first human embryonic stem cell line in 1998 (Thomson et al., 1998). Patient-matched embryonic stem cell lines can now be derived using somatic cell nuclear transfer (SCNT). However, since the generation of embryonic stem cells involves the destruction of the embryo, there has been much controversy surrounding their use.



In 2006, Shinya Yamanaka converted somatic cells into Induced pluripotent stem cells by introducing four specific genes collectively known as encoding transcription factors (Myc, Oct3/4, Sox2, and Klf4) (Takahashi & Yamanaka, 2006). Induced pluripotent stem cells (also known as iPS cells or iPSCs) are a type of pluripotent stem cell that can be generated directly from a somatic cell. Since iPSCs can be derived directly from adult tissues, they not only bypass the need for embryos but can be made in a patient-matched manner, which means that each individual could have their own pluripotent stem cell line. These unlimited supplies of autologous cells could be used to generate transplants without the risk of immune rejection.

In 2013, Shoukhrat Mitalipov made the first embryonic stem cell from human skin cells by reprogramming human skin cells back to their embryonic state (Tachibana et al., 2013). In 2014 Young Gie Chung used skin cells from adult patients to generate genetically matched stem cells of each individual (Chung et al., 2014). Derrick J. Rossi reprogrammed mature blood cells from mice into blood-forming hematopoietic stem cells using transcription factors (Riddell et al., 2014). Douglas Melton generated mature human insulin-producing pancreatic beta cells from stem cells in vitro, which, when transplanted into mice, secrete insulin appropriately in response to glucose levels (Pagliuca et al., 2014). In 2014, Human embryonic stem cells restored the sight of 18 patients with severe vision loss as a result of two types of macular degeneration (Schwartz et al., 2015). In 2018, Tippi MacKenzie performed first in utero prenatal stem cell transplantation of a woman's stem cells into her growing fetus with alpha thalassemia, leading to the live birth of an infant with a normally fatal fetal condition.

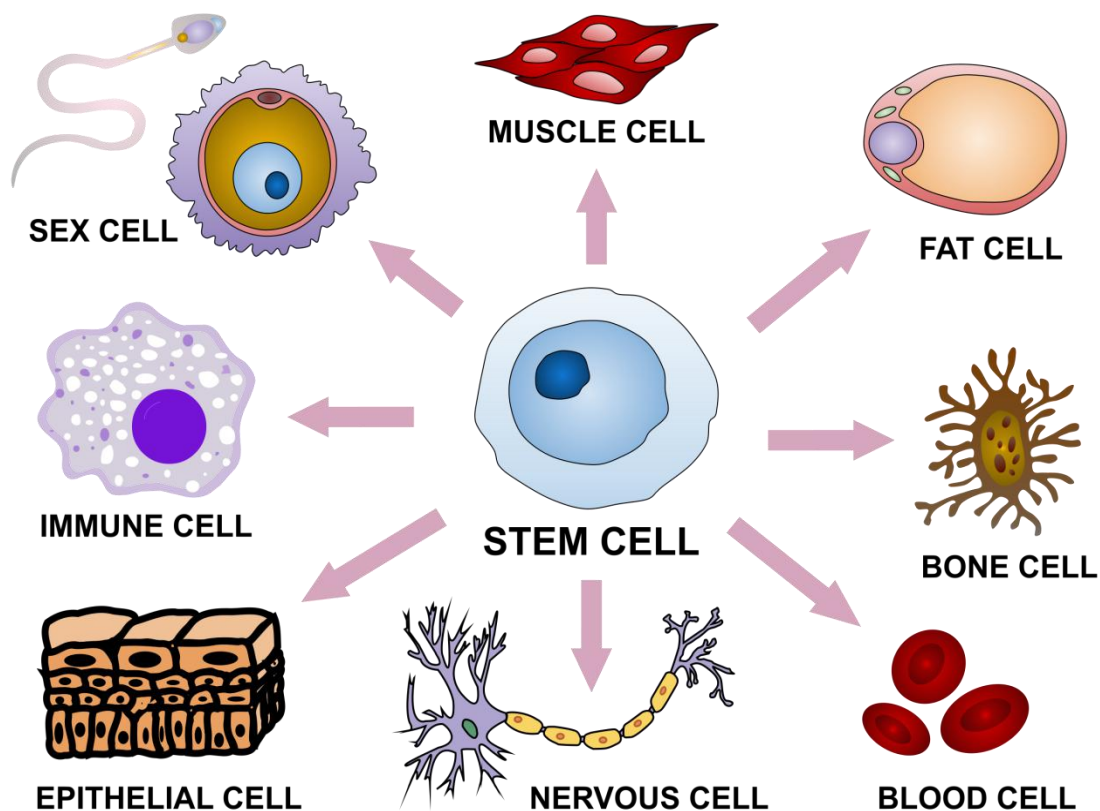


Fig. 10. Stem cells are able to change and differentiate into other types of body cells (Haileyfournier/CC BY-SA 4.0)

### 3D Bioprinting

3D printing is an additive technology in which objects are built up in a great many very thin layers. The first commercial 3D printer was based on a technique called stereolithography which was invented by Charles Hull in 1984. 3D Printing was first used for medical purposes as dental implants and custom prosthetics in the 1990s. Bioprinting is a technique that is used to develop cellular structures using bioinks filled with stem cells. The biomaterial is applied layer by layer to produce skin, tissue, or even an organ. The objective is to make these tissues and organs suitable for transplantation and to provide long-term effective solutions. In 1996, Gabor Forgacs noted that cells can be combined into completely new, spatial structures (Foty et al., 1996). In 2001, the first lab-grown organ (a bladder) created with a spatial scaffold was implanted in a human. The scaffold was colonized with the recipient's host cells so as to rule out a potential problem with the rejection of the "bred" organ by the patient's immune system. In 2003, W Cris Wilson Jr and Thomas Boland developed the first bioprinter that was a modified office inkjet printer that bioprint with biological materials and deposit cells as opposed to ink (Wilson & Boland, 2003). In 2004, Gabor Forgacs developed a bioprinter that allowed 3D direct biodegradation without the need to build scaffolding. The first commercial 3D bioprinter (NovoGen MMX) was launched by Gabor Forgacs founded company Organovo in 2009. In 2010, FDA approved the first 3D printed orthopedic implants. The first 3D bioprinted kidney was developed in 2011. In 2013, the first bioprinted, bioengineered ears were developed that looks and acts like a natural ear (Reiffel et al., 2013). First 3D printed skull transplant was done in 2014. In 2015, a swatch of tissue containing skin cells interwoven with structural material that can potentially function as blood vessels were created. In 2017, a 3D printed bioprosthesis ovary was developed that restores ovarian function in sterilized mice (Laronda et al., 2017). Lattice Medical developed 3D-printed breast implants in 2017 that dissolve after a year and allow adipose tissue to naturally regenerate. The first 3D-printed spinal implants were approved by FDA in 2017 to treat multiple injuries in the spine. First Auricular Reconstruction by in vitro regeneration of patient-specific ear-shaped bioprinted cartilage was done in five children with unilateral microtia in 2018 (Guangdong et al., 2018). The First 3D-printed human corneas were developed in 2018 (Isaacson et al., 2018). Poietis started marketing the first commercial bioprinted human full skin model made by laser-assisted bioprinting in 2018. In 2019 first 3D-bioprinted bioengineered heart was developed with human tissue, about the size of a rabbit's heart, with cells, blood vessels, ventricles, and chambers (Noor et al., 2019). In the same year, there was also the development of 3D bioprinted human liver organoids that performed all of the liver's typical functions.

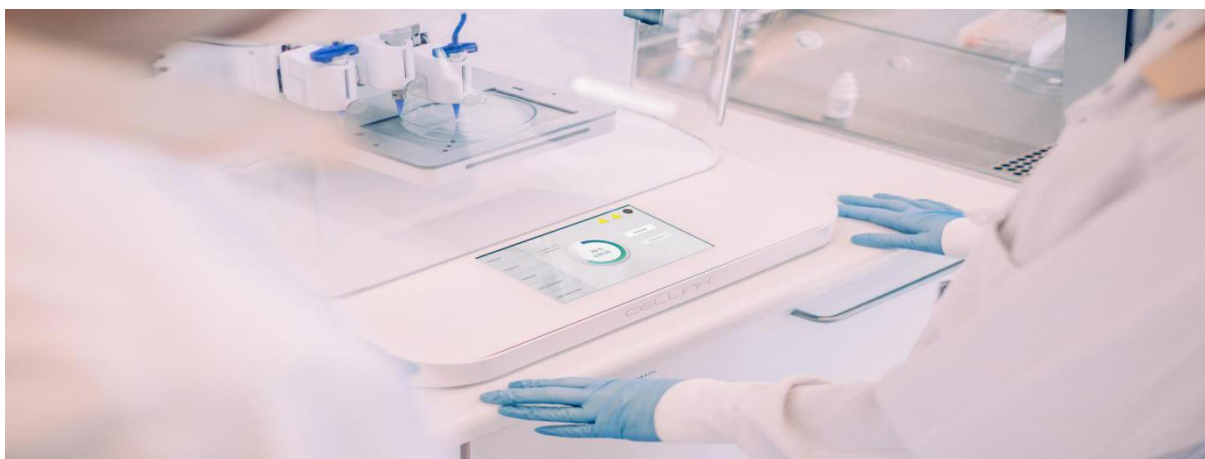


Fig. 11. Bioprinting on a bioprinter (Philip Ezze/CC BY-SA 4.0)

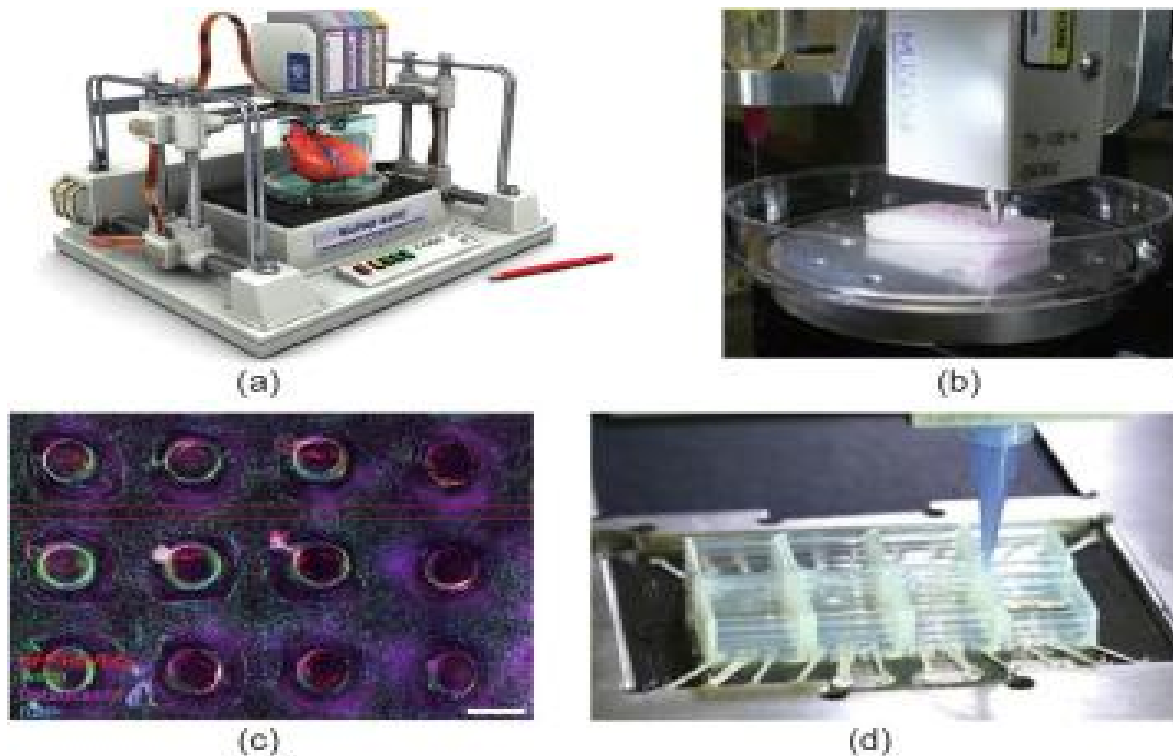


Fig. 12. Applications of 3D bioprinting technology

(a) 3D bioprinter, (b) 3D bioprinting solid tissue, (c) 3D bioprinting hollow tissue, (d) 3D bioprinting of organs-on-chips (Zhang et al.,2019/CC BY-SA 4.0)

### **Magnetic Resonance Imaging & Functional Magnetic Resonance Imaging**

Magnetic resonance imaging (MRI) originally called NMRI (nuclear magnetic resonance imaging) is a medical imaging technique and a medical application of nuclear magnetic resonance (NMR) that uses strong magnetic fields, magnetic field gradients, and radio waves to generate images of the organs in the body. Raymond Damadian discovered that hydrogen signal in cancerous tissue is different from that of healthy tissue and this difference could help in tumor detection by nuclear magnetic resonance (Damadian, 1971). He built the first MRI scanner and achieved the first MRI scan of a human. Paul Lauterbur produced the first NMR image of a test tube. Peter Mansfield improved mathematics behind MRI and developed the echo-planar technique, which allowed images to be produced in seconds and later became the basis for fast MR imaging. In 1980, Raymond Damadian produced the first commercial MRI scanner through his company, Fonar (Field Focused Nuclear Magnetic Resonance). Damadian's "focused field" technology proved significantly less efficient and slower than Lauterbur's gradient approach. Fonar eventually abandoned Damadian's technique in favor of the methods adopted by Paul Lauterbur. MRI has a wide range of applications in medical diagnosis. 50,000 MRI scanners are estimated to be in use worldwide that are used mostly for Brain and spine examination (Rinck, 2019).

Functional magnetic resonance imaging (fMRI) or detection of the regional brain activity using MRI by imaging the change in hemodynamic response related to energy use by brain cells, tracks the areas of the brain that are activated by tracking changes in the oxygen levels and blood flow in the brain. Inside an MRI scanner, the patient is asked to perform a simple task. The more brain activity in one area, the more oxygen will be used resulting in more blood flow to that area. The first attempt to detect the regional brain activity using MRI was performed by Belliveau using the contrast agent Magnevist, however, this method

is not popular in human fMRI. In 1992, Kenneth Kwong and colleagues, using the BOLD (Blood Oxygen Level Dependent) contrast and both gradient-echo and inversion recovery echo-planar imaging (EPI) sequence at a magnetic field strength of 1.5 T published studies showing clear activation of the human visual cortex because both blood flow and blood volume increased locally during activity in neural tissue (Kwong et al., 1992). Ogawa and Bandettini conducted similar studies in 1992. These techniques are still used in current-day fMRI studies. Currently, more slices using stronger magnetic gradients are used to collect data that is analyzed by statistical techniques.

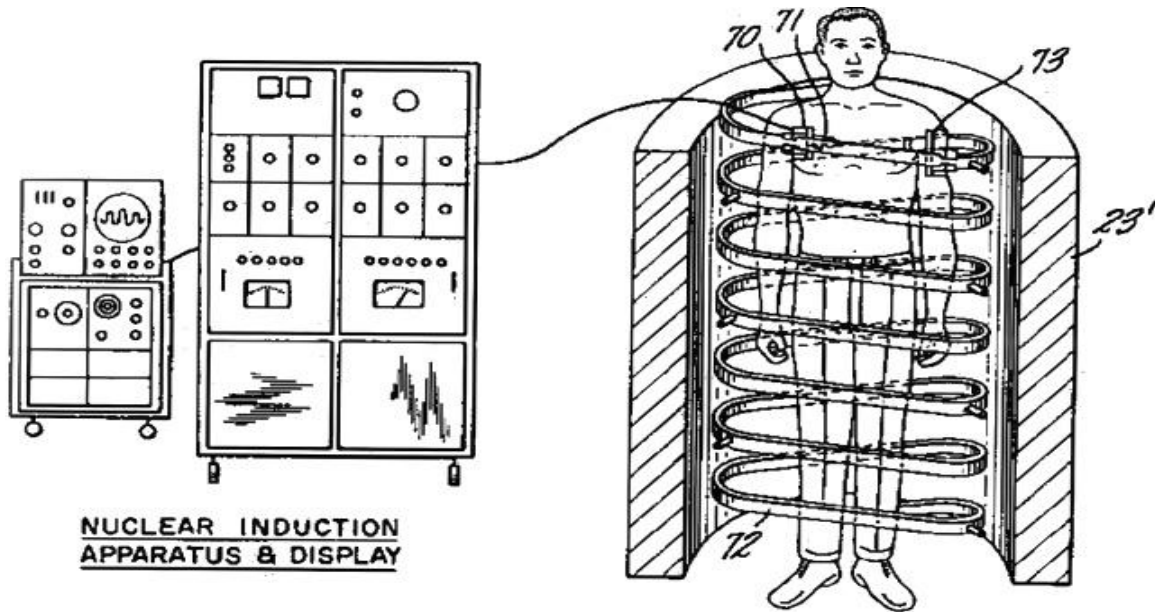


Fig . 13. Raymond Damadian's "Nuclear Induction Apparatus for detecting cancer in tissue."



Fig. 14. Functional magnetic resonance imaging at the Imperial Centre for Psychedelic Research (Thomas Angus/CC BY-SA 4.0)

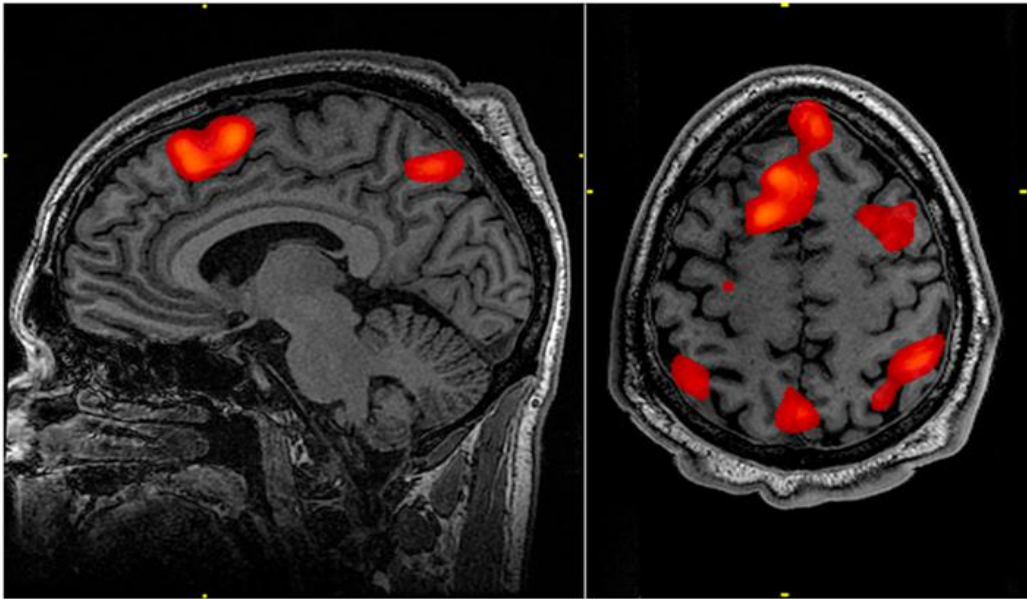


Fig. 15. fMRI scan during working memory tasks. Working memory tasks typically show activation in the bilateral and superior frontal cortex as well as in parts of the superior bilateral parietal cortex (Graner et al., 2013)

### Neurostimulation

In 2010, Senza spinal cord stimulation (SCS) system was approved in European Union for chronic pain treatment. The first implanted neurostimulation device obtained a CE Mark approval in 2010 to treat chronic migraine. In 2013, the first closed-loop, brain-responsive neuromodulation system (RNS System) was launched to prevent epileptic seizures. In 2017, the first person to receive deep brain stimulation (DBS) for stroke recovery regained motor function. FDA approved the first percutaneous peripheral nerve stimulation systems SPRINT® endura™ (single lead) and extensa™ (dual lead) in 2018 for treating chronic and acute pain, including post-operative and post-traumatic pain. A Pivotal Study in 2019 demonstrated Evoke® Evoked compound action potential-controlled closed-loop stimulation provided significantly greater and more clinically meaningful pain relief up to 12 months compared to open-loop spinal cord stimulation to patients with chronic intractable back and leg pain (Mekhail et al, 2020).

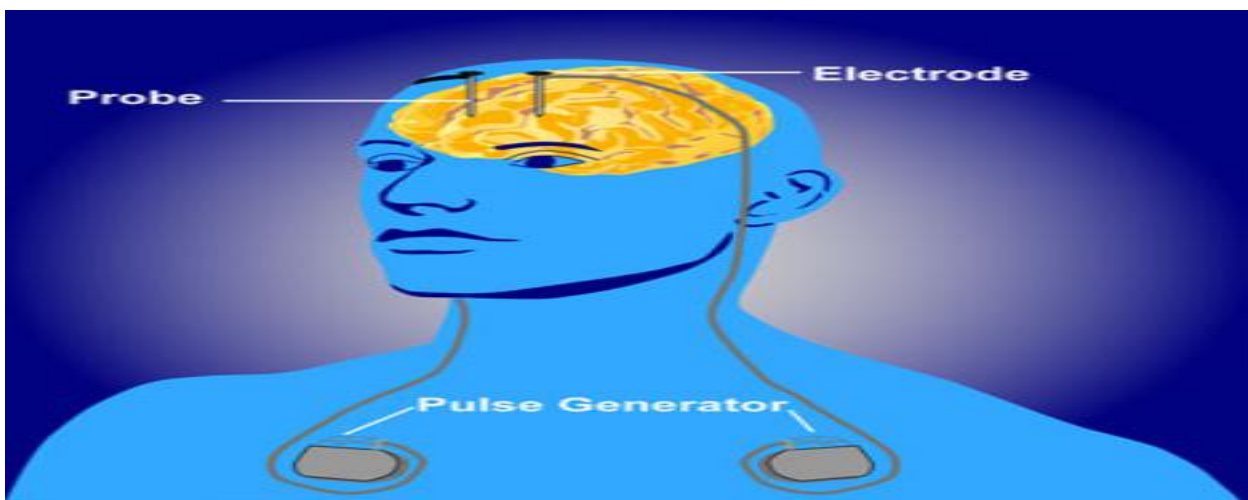


Fig. 16. Deep brain stimulation

## Cochlear Implant

A cochlear implant is a surgically implanted electronic device that delivers a modified sense of sound to a person with sensorineural hearing loss by bypassing and replacing the typical acoustic hearing process with electric signals that stimulate the auditory nerve directly. Intensive auditory training may help a person with a cochlear implant in interpreting those signals as sound and speech. In 1980, making hearing a reality for deaf people, William House implanted the first cochlear implant in a child using a single-channel cochlear implant. Around the same time, Paul Trainor began developing a multiple-channel cochlear implant that was first implanted in a human in 1982. FDA approved the single channel cochlear implant for deaf adults in 1984. In 1985, multiple-channel cochlear implant was approved by the FDA for post lingual deaf adults, who had hearing before going deaf. In 1990, multiple-channel cochlear implant was approved by FDA for children from two to 18 years of age (Clark, 2006).

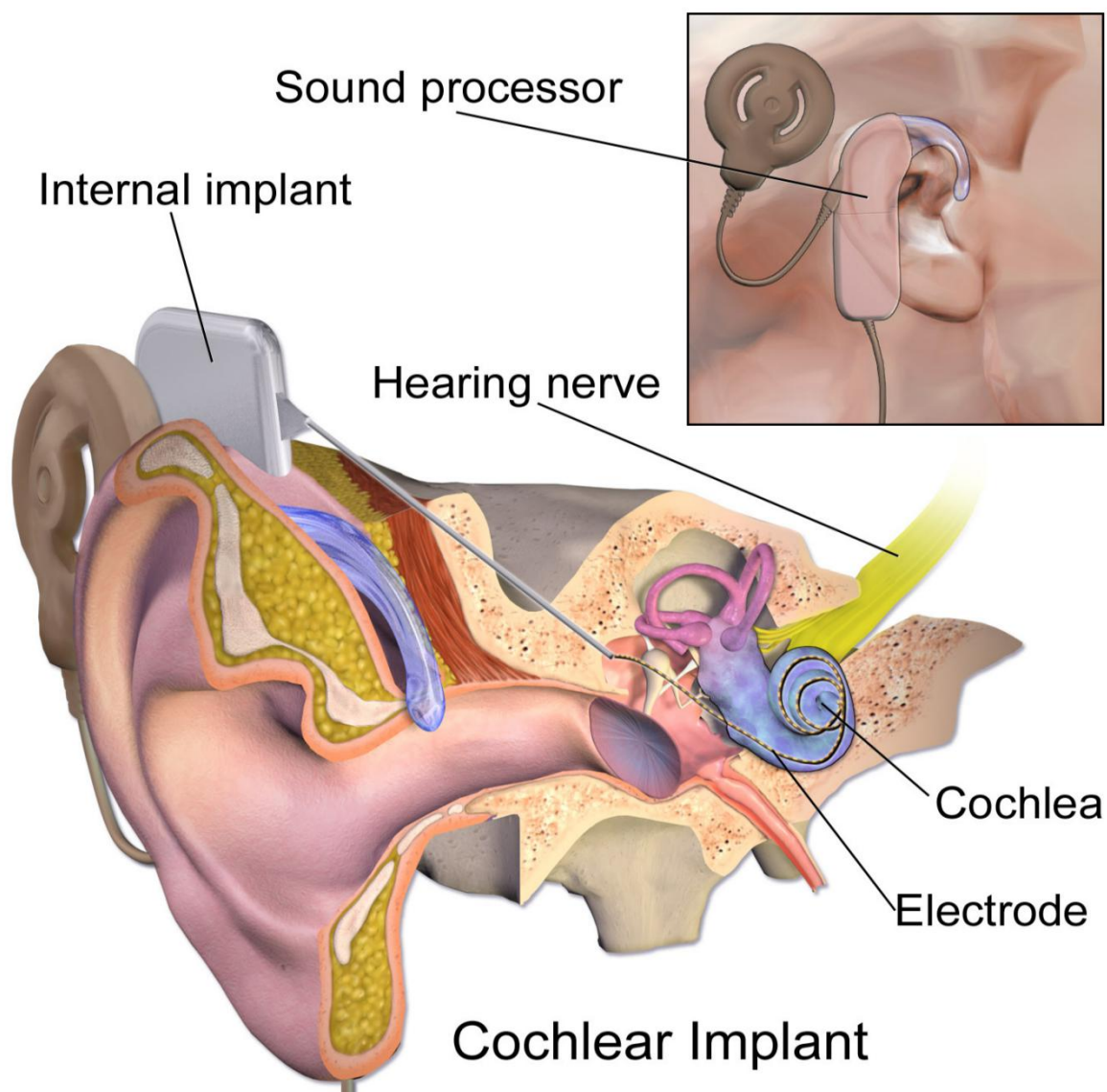


Fig. 17. Cochlear Implant (Blausen Medical/CC BY 3.0)

## Intravascular Stenting

A stent is a metal or plastic tube inserted into the lumen of an anatomic vessel or duct to keep the passageway open. The first intravascular stent was named Wallstent after its inventor's name Hans Wallstén. In 1986, Jacques Puel and Ulrich Sigwart inserted the first intravascular stent, Wallstent, for the first time into a human coronary artery (Roguin, 2011) (Sigwart et al, 1987) (Serruys & Strauss, 1992). It was used to prevent the vessel from closing and to prevent restenosis in coronary surgery. Julio Palmaz and Richard Schatz worked together and performed extensive studies on a balloon-expandable stent for coronary use to solve problems that were not solved by balloon angioplasty. In 1987, the first Palmaz-Schatz coronary stent was implanted. FDA approved Palmaz-Schatz Balloon Expandable Stent in 1994. Drug-eluting stents are metal stents that elute a drug designed to limit the growth of neointimal scar tissue, thus reducing the likelihood of stent restenosis. In 2003, the first drug-eluting stent (CYPHER Sirolimus-Eluting Coronary Stent) was approved by FDA. In 2004, a paclitaxel-eluting stent (Taxus Express paclitaxel-eluting coronary stent) was approved by FDA. Clinical trials show that Stent implantation can significantly reduce the incidence of restenosis. With the use of drug-eluting stents, the incidence of in-stent restenosis remains below 10% (Fontos, 2006).

## Stent in Coronary Artery

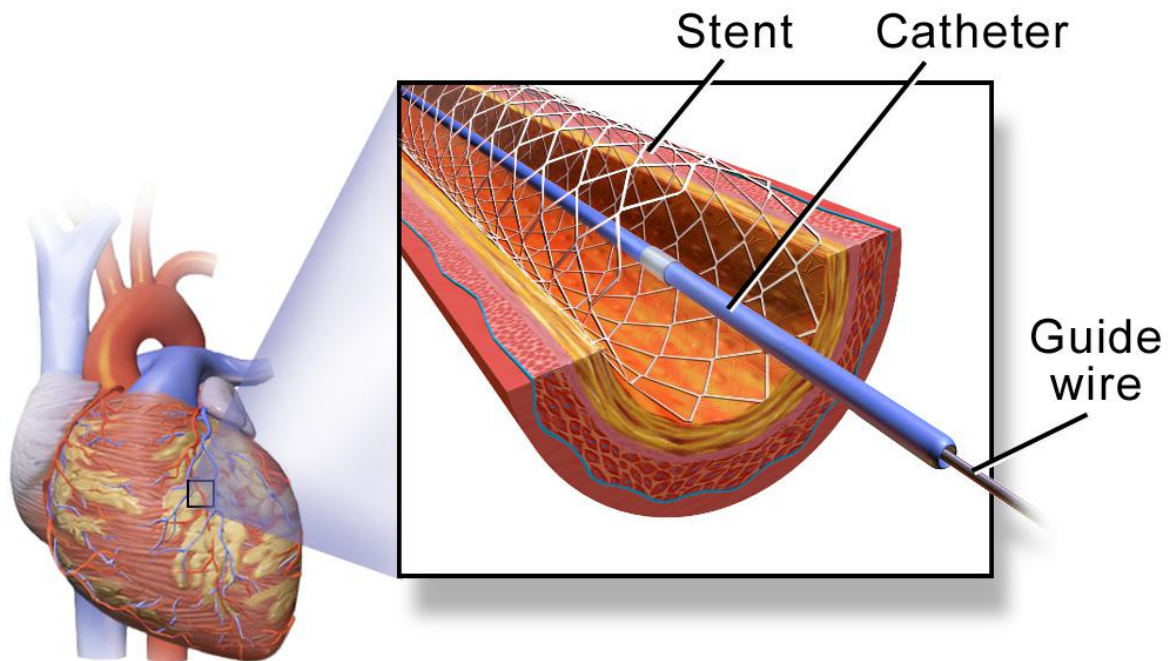


Fig. 18. Stent in Coronary Artery (Blausen Medical 2014/CC BY 3.0)

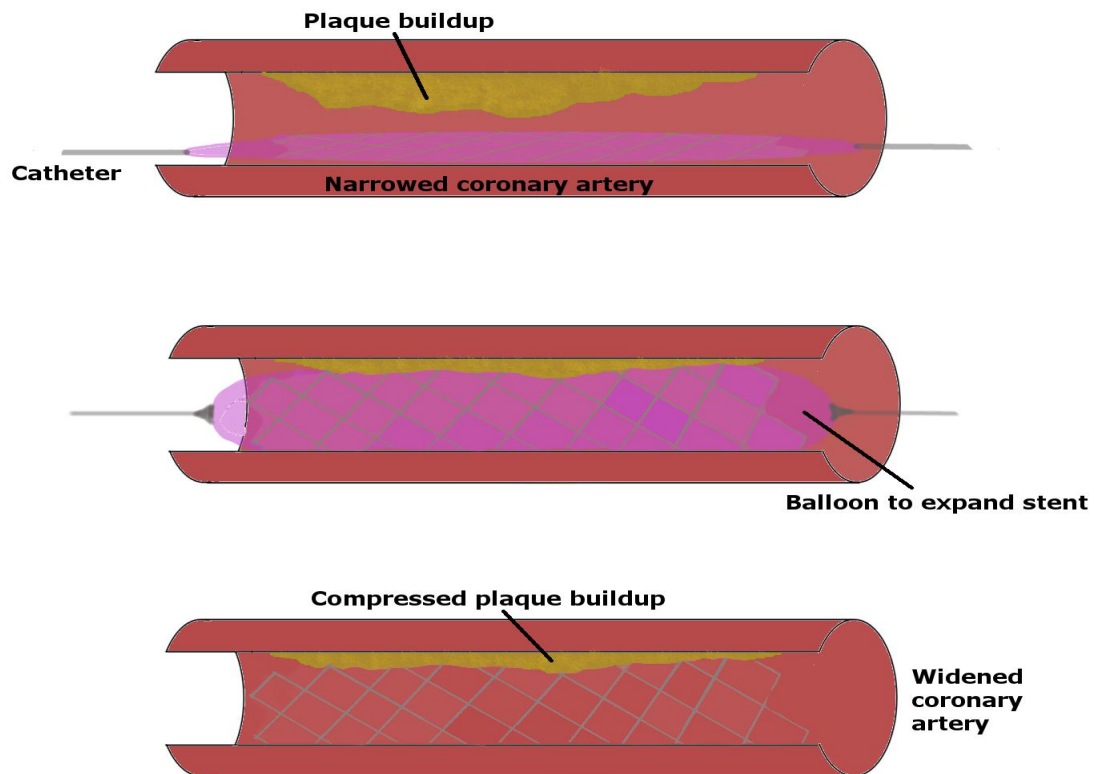


Fig. 19. Coronary stent inserted and expanded in a coronary artery (ETTon/CC BY-SA 4.0)

### Cardiac Valves Percutaneous Replacement and Repair

Cardiac surgery today is less invasive with catheters now assisting in heart valve replacement and repair especially for those whose risks prohibited them from open-heart surgery. Performed percutaneously via a catheter through the skin, many cardiac procedures no longer require an open heart surgery approach. These procedures include replacements and repair of heart valves.

Transcatheter valve replacement is a minimally invasive surgical procedure that replaces and repairs damaged heart valves. In 2011, Sapien Transcatheter Aortic Heart Valve was approved by FDA for Transcatheter aortic valve replacement (TAVR) in patients requiring replacement of aortic valve but not eligible for open-heart surgery. In 2017, Sapien 3 transcatheter heart valve device was approved by FDA for transcatheter Mitral Valve replacement. In 2018, the first implant of the PASCAL transcatheter valve repair system was performed in a patient with tricuspid regurgitation. FDA approved PASCAL transcatheter valve repair system in 2020 for the treatment of both mitral valve and tricuspid valve.

Mitral regurgitation is treated either by mitral valve repair or replacement surgery. MitraClip (mitral clip) is a medical device used for percutaneous mitral valve repair which is a minimally invasive technique to treat mitral valve regurgitation for individuals who



should not have open-heart surgery. It is implanted via a tri-axial transcatheter technique and involves suturing together the anterior and posterior mitral valve leaflets. MitraClip was approved by FDA in 2013 to reduce mitral regurgitation in patients whose significant mitral regurgitation and heart failure symptoms resulted from abnormalities of the mitral valve and whose risks prohibited them from mitral valve surgery. Transcatheter tricuspid valve repair using the MitraClip is an option for patients with severe tricuspid regurgitation. In a multicenter study, 64 patients underwent MitraClip implantation with a 97% procedural success. Significant reductions in effective regurgitant orifice area and regurgitant volume were observed (Nickenig et al., 2017).

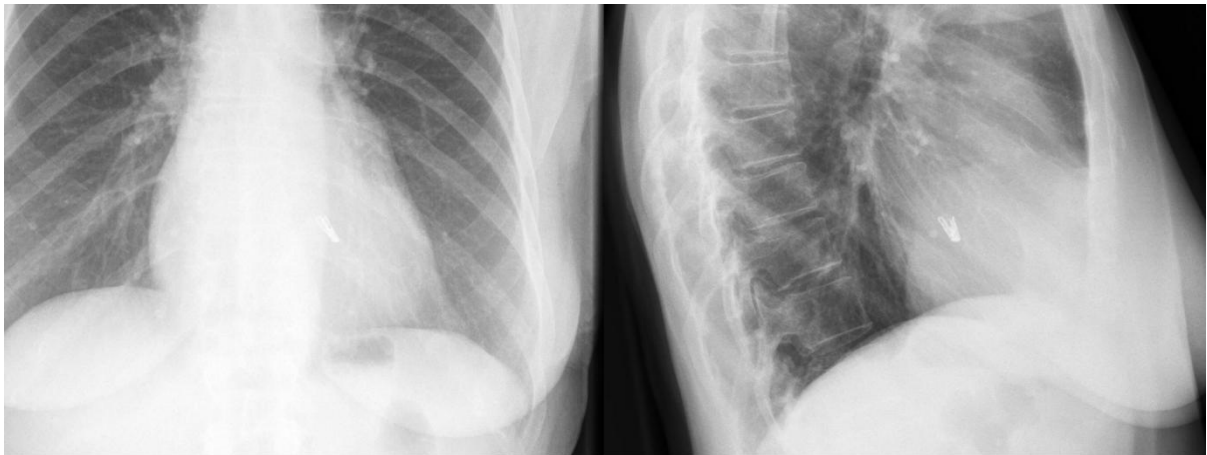


Fig. 20. MitraClip in the X-ray image (Hellerhoff/CC BY-SA 3.0)



Fig. 21. PASCAL transcatheter valve repair system for the treatment of mitral regurgitation

(Hellerhoff/CC BY-SA 4.0)

## Artificial Intelligence

Artificial intelligence (AI) is defined as the ability of computer algorithms to make educated guesses based purely on input data. The use of machine-learning algorithms and software, or artificial intelligence (AI), to replicate human cognition in the analysis, display, and comprehension of complicated medical and healthcare data is how artificial intelligence is used in healthcare. The ability to gather data, process it, and provide a well-defined output to the end-user distinguishes AI technology from traditional healthcare technologies. Machine learning techniques and deep learning are used by AI to do this. These algorithms are capable of recognizing patterns in human behavior and developing their own logic. Machine learning models must be trained with a large amount of data to gain relevant insights and predictions. Artificial intelligence algorithms are literal. Once a goal is established, the algorithm learns only from the input data and can only comprehend what it has been designed to do. Some deep learning algorithms can predict with exceptional precision but provide little to no clear explanation for the logic behind their judgments other than the data and method type used.

In 1986, the first version of DXplain was developed. DXplain is an artificial intelligence decision support system that uses inputted symptoms to generate a differential diagnosis and also serves as an electronic medical textbook, providing detailed descriptions of diseases and additional references (Barnett et al., 1987). The first commercial Computer-Aided Diagnosis (CAD) system for mammography, the ImageChecker M1000 system was approved by FDA in 1998. In 2011 Nuance Communications and WellPoint partnered with IBM to utilize clinical decision support capabilities of Watson, a Deep QA artificial intelligence supercomputer that was developed by IBM. In 2011, FDNA Inc. developed artificial intelligence-based phenotyping technology (Facial Dysmorphology Novel Analysis). In 2012, the first deep convolutional neural network for structure-based drug discovery was developed by Atomwise, Inc. Pharmabot, a pediatric generic medicine consultant chatbot designed to prescribe, suggest and give information on generic medicines for children was developed in 2014 (Comendador et al., 2015). In 2016, IBM developed Medical Sieve, an automated cognitive assistant for radiologists and cardiologists to help in clinical decision-making (Syeda-Mahmood et al., 2016). Mandy, a primary care chatbot system was created in 2017 to assist healthcare staff by automating the patient intake process (Ni et al., 2017). An AI-enabled Life Coach with an AI chatbot (Wysa) was launched for mental and emotional wellness in 2017. In 2017 FDA approved the first Medical Imaging Analytics Cloud Software With Deep Learning (Arterys Cardio DL) for Cardiac MRI. The first artificial intelligence medical device to detect diabetic retinopathy in adults who have diabetes (IDx-DR) was approved by FDA in 2018.

In a study in 2018, Skin cancer was detected more accurately by a deep learning convolutional neural network artificial intelligence system than by dermatologists. Artificial intelligence system that was taught to distinguish malignant moles from benign ones found 95% of melanomas compared to 86.6% for dermatologists (Haenssle et al., 2018). Google developed an artificial intelligence system in 2019 that detects lung cancer more accurately than human radiologists. Analyzing a single CT scan, the AI model detected lung cancers 5 percent more often than the experts and was 11 percent more likely to decrease the rate of false positives (Ardila et al., 2019). A study in 2020 showed that the AI model with Google DeepMind algorithm could predict breast cancer with the same level of accuracy as a single expert radiologist. Compared to human experts, the system saw a reduction in false positives and in false negatives. AI model performed better than a single radiologist and was "non-inferior" versus two (McKinney et al., 2020). Another study in 2020 reported the successful development and deployment in clinical practice of an

AI-based algorithm to accurately detect, grade, and evaluate prostate cancer with 98% sensitivity and 97% specificity (Pantanowitz et al., 2020).

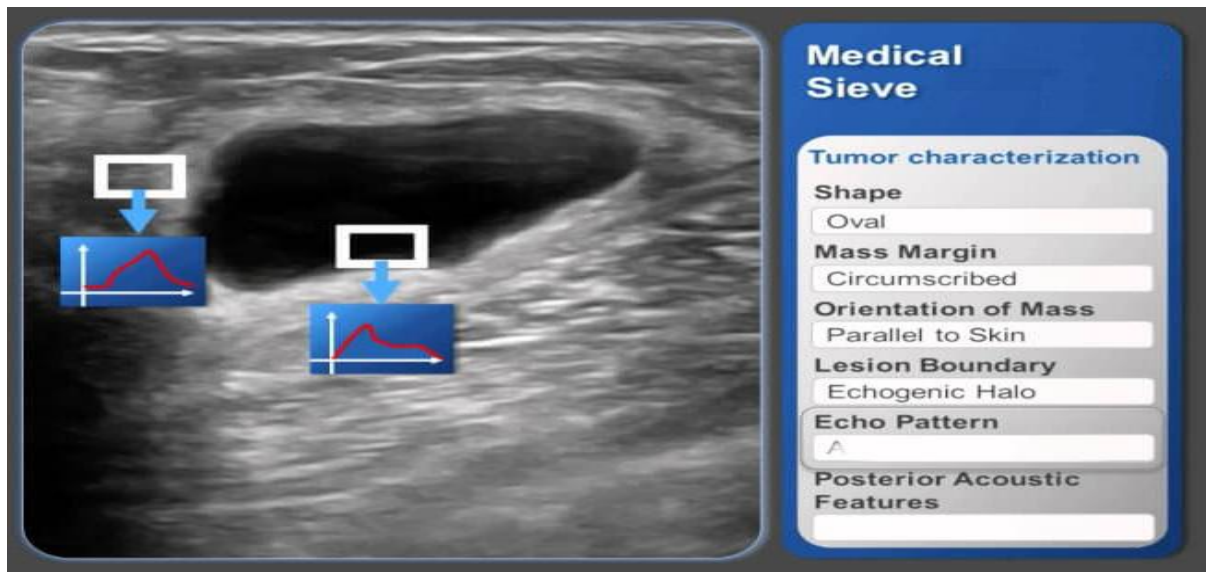


Fig. 22. Medical Sieve- An Artificial Intelligence algorithm launched by IBM to assist in clinical decision making in radiology and cardiology (The Medical Futurist/CC BY 4.0)

## Bionics

Bionics or biologically inspired engineering means incorporating the knowledge of biological processes and systems to design engineering systems and technologies. The first commercially available bionic hand (i-LIMB hand) was launched by Touch Bionics in 2007. In 2013, Touch Bionics invented a prosthetic hand (i-limb ultra revolution) that can be controlled via iPhone with the 'bioism' mobile app. An assistive exoskeleton allowing people with spinal cord injuries to stand upright, walk and climb stairs controlled by a wrist-mounted remote (ReWalk device ) was approved by FDA in 2011. The first Bionic eye, Argus® II Retinal Prosthesis System was approved by FDA in 2013 for patients who have no vision or almost no vision due to advanced retinitis pigmentosa.



Fig. 23. i-limb: World's first bionic prosthetic hand (Danie Ware/CC BY 2.0)



Fig. 24. Bionic Limbs (Cpl Richard Cave RLC/MOD/OGL v1.0)



Fig. 25. Ballroom dancer Adrienne Haslet-Davis debut performance after she lost her left leg in the 2013 Boston Marathon bombing. MIT Professor Herr who himself had lost both legs from frostbite in a rock climbing accident launched a 200-day research study of the dynamics of dance and embedded the fundamentals of dance into a bespoke bionic limb (Steve Jurvetson/CC BY 2.0)

## Robotic Surgery and Tele Surgery

In 1983, the first surgical robot "Arthrobot" was developed and used. Arthrobot assisted by manipulating and positioning the patient's leg on voice command. The first completely robotic surgical system (da Vinci Surgical System) was approved by FDA in 2000 for use in laparoscopic procedures. The da Vinci surgical system due to its microchip technology and 3-D optics made it possible to treat a broader range of conditions with a minimally invasive approach enabling surgeons to perform complex procedures by making tiny incisions. The DigiMatch ROBODOC Surgical System was approved by FDA in 2008 for assisting the physicians with presurgical planning and implementation of the presurgical plan for femoral canal preparation in primary total hip arthroplasty. In 2001, the first telesurgery (Lindbergh Operation) was performed by Jacques Marescaux and his team located in New York on a patient in Strasbourg, France using high-speed telecommunications services and Zeus surgical robot.

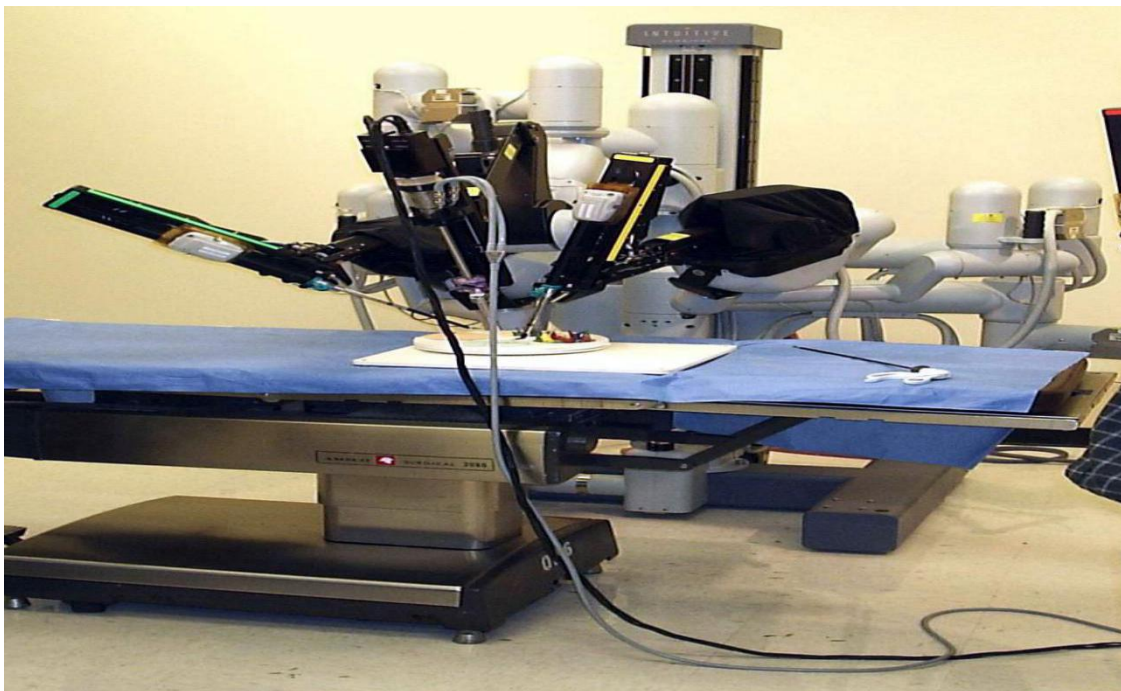


Fig 26. da Vinci surgical system (Nimur/CC BY-SA 3.0)



Fig. 27. DaVinci™ robotic system docked to the patient (Poffo et al.,2013/CC BY 4.0)

## Capsule Endoscopy and Natural Orifice Endoscopic Surgery

Capsule endoscopy is used to examine parts of the gastrointestinal tract that cannot be seen with other types of endoscopy. It consists of a capsule that contains a tiny camera and an array of LEDs powered by a battery. After swallowing, the capsule passes along the gastrointestinal tract taking a number of images per second which are transmitted wirelessly to a portable recording device. In 2001, FDA for the first time approved endoscopy capsule.

Natural Orifice Transluminal Endoscopic Surgery is endoscopic surgery performed through natural orifices. This technique allows access to the peritoneal cavity through natural orifices without passing through the anterior abdominal wall. First Natural Orifice Transluminal Endoscopic Surgery was performed by G.V. Rao and D.N. Reddy in 2004, which they later presented at the World Congress of Gastroenterology (Reddy & Rao, 2004) (Rao & Reddy 2006). They carried out a transgastric appendectomy in a male patient with severe burn lesions in his abdominal wall using a conventional flexible endoscope.



Fig. 28. Capsule endoscopy (TMKO/CC BY 3.0)



Fig. 29. Cmdr. Gordon Wisbach prepares to insert an endoscope through a patient's belly button before performing a natural orifice endoscopic surgery

## Medical Lasers

Patricia Era Bath patented Laserphaco Probe and utilized it for the first Laser Cataract Surgery (PhotoAblative Cataract surgery) in 1988. In 1990, Derma-lase marketed Q-switched lasers for scar-free removal of pigmented lesions and tattoos. Excimer laser (Exeimed UV200LA and SVS Apex) was approved by FDA in 1995 for Phototherapeutic Keratectomy.



Fig. 30. Diabetic retinopathy laser surgery



Fig. 31. Laser Tattoo Removal using Q-switch laser (Alice Pien/CC BY-SA 4.0)

## Transplants

During the last 40 years, transplant procedures have become more inventive. The first human heart-lung combined transplant was performed in 1981. In 1989, there was the first Living-Donor Liver Transplant. The first long-term successful hand transplant was carried out in 1999. The world's first quadruple transplantation of four organs from a single donor (a kidney, two lungs, and a heart) to four recipients happened in 2000. The first partial face transplant was done in 2005. In 2010, the first full-face transplant was carried out on a man who severely damaged his face in an accident, giving him a new nose, lips, teeth, and cheekbones during 24 hours of surgery. In 2011, the first successful uterus transplant was done from a deceased donor. The first successful penis transplant was carried out in 2014. In 2018, a penis transplant was done with an injection of the bone marrow cells from the donor to speed recovery and prevent rejection.

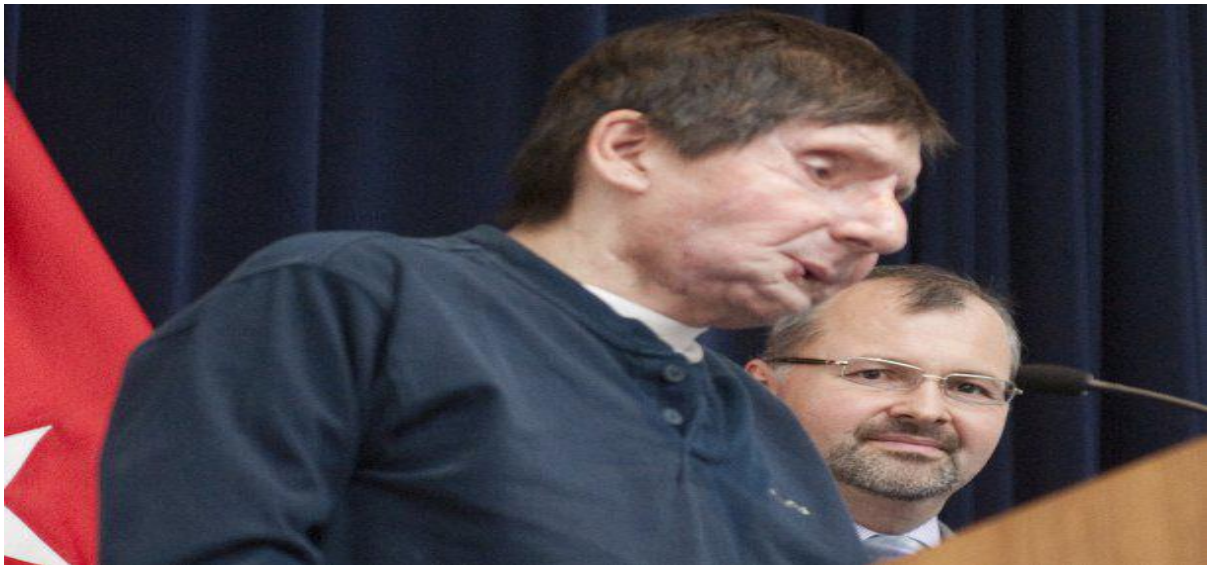


Fig. 32. Second US partial face transplant recipient Jim Maki (left) with his surgeon Bohdan Pomahač who performed the first US full face transplant

## HIV Management

In 1987, Zidovudine was approved as the first treatment for HIV by FDA. In 1996, Indinavir-based triple-drug therapy for AIDS, HAART (highly active antiretroviral therapy) was incorporated into clinical practice to treat HIV making HIV manageable as a chronic disease. In 2006, FDA approved Atripla that combined three antiretroviral drugs into one daily pill. In 2012, FDA approved the Truvada (Emtricitabine/ Tenofovir) combination pill for use as pre-exposure prophylaxis (PrEP) for HIV, based on growing evidence that the drug was safe and effective at preventing HIV in populations at increased risk of infection. Stribild, a one-dose combination of four HIV medications (cobicistat, elvitegravir, emtricitabine, and tenofovir) was approved by FDA in 2013. In 2021, FDA approved Cabenuva, the first extended-release, monthly administered, complete drug regimen (cabotegravir and rilpivirine, injectable formulation) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults. FDA approved the First extended-release injectable pre-exposure prophylaxis, Apretude (cabotegravir extended-release injectable suspension) in 2021 to reduce the risk of sexually acquired HIV in at-risk adults and adolescents.





Fig. 33. Stribild, a one dose combination of four HIV medications (JörgenMoorlag/CC BY-SA 4.0)

### Cure for Hepatitis C

Hepatitis C is an infectious disease caused by the hepatitis C virus (HCV) that primarily affects the liver. It often leads to liver disease and occasionally cirrhosis. In some cases, those with cirrhosis will develop serious complications such as liver failure, liver cancer, or dilated blood vessels in the esophagus and stomach. PEGylated interferon alfa-2b was approved by FDA in 2001 for the treatment of chronic hepatitis C. PEGylated interferon alfa-2a was approved by FDA in 2002 for the treatment of adults with chronic hepatitis C with compensated liver disease. At that time, PEGylated interferon in combination with ribavirin was the standard regimen used in the management of hepatitis C. The cure rate was less with greater side effects and a heavy anti-viral-drug one-year treatment program. In 2013, Sofosbuvir, with a 95% cure rate in 12 weeks of combination therapy was approved by FDA for Hepatitis C. FDA also approved Simeprevir in 2013 for combination therapy of hepatitis C with a once-daily oral dose for 12 weeks and cure rates of the 80s to 90s. Although sofosbuvir and simeprevir are expensive, chronic infection can be cured more than 95% of the time with antiviral medications such as sofosbuvir or simeprevir (Majumdar et al., 2016).



Fig. 34. A combination pill of Sofosbuvir and Daclatasvir to treat hepatitis C

## Glucose Monitoring and Human Insulin

First Personal Glucose Meter (Dextrometer) was invented in 1980 for home blood glucose monitoring that allowed people with diabetes to check blood glucose in about one minute. The first continuous glucose monitor (Continuous Glucose Monitor System) was manufactured by Medtronic MiniMed and was approved by FDA in 1999. The device was intended to help physicians establish patients' glucose profiles and monitor insulin therapy. In 2001, FDA approved the first real-time continuous glucose monitor GlucoWatch Biographer. While the armband-based device was noninvasive, it was not widely successful because it tended to cause site irritation. In 2004, Dexcom introduced its first real-time continuous glucose monitor. Currently, the Dexcom Continuous Glucose Monitoring system has a body sensor with a dedicated Apple Watch app, a Samsung Galaxy Watch app, and a WearOS app that can track and display glucose levels in the form of a graph. In 2017, FDA approved FreeStyle Libre Flash Glucose Monitoring System, the first continuous blood sugar monitor for diabetics that doesn't need backup finger prick tests. It uses a small sensor attached to the upper arm. A Saliva Glucose Biosensor was developed in 2016 for a pain-free and non-invasive, saliva-based glucose test with a small, disposable strip, which when exposed to an individual's saliva instantly provides a glucose measurement.

In 1982, Human insulin (Humulin) was approved by FDA. In 1985, the first insulin pen injector was launched (Rex et al, 2006). National Institute for Health and Care Excellence (NICE) endorsed insulin pumps in the United Kingdom in 2003. An insulin pump replaces slow-acting insulin with a continuous infusion of rapid-acting insulin. A bolus dose is delivered after meals or to correct a high blood glucose level and a basal dose is delivered continuously at an adjustable basal rate. In 2016, FDA approved first automated insulin delivery device (MiniMed 670G) for type 1 diabetes, an artificial pancreas device system that automatically monitors a person's blood sugar levels and supplies insulin when needed.



Fig. 35. Self Monitoring of Blood Glucose by Glucometer (Omstaal/CC BY-SA 4.0)



Fig. 36. Dipisulin containing Human Insulin and Human-Made Insulin (NPH)(Reza babaeian/(CC BY-SA 3.0)



Fig. 37. Administration of insulin with an insulin pen



Fig. 38. Insulin pump with infusion set

## Vaccines

The first commercial Hepatitis B Vaccine (Heptavax) was licensed in the USA in 1981. Maurice Ralph Hilleman invented Heptavax by treating blood serum with pepsin, urea, and formaldehyde. In 1986, the first recombinant virus-like particle-based vaccine for Hepatitis B, Engerix-B was approved in Belgium. In 1991, the first vaccine for hepatitis A (Havrix) was approved in Europe. FDA approved the first vaccine for Lyme disease (LYMERix) in 1998. In 2006, the first human papillomavirus vaccine Gardasil was approved by FDA. In 2007, the second rotavirus vaccine was approved (the previous vaccine was withdrawn within 1 year because of its association with intussusception). 6-in-1 vaccine (VAXELIS) with Diphtheria and Tetanus Toxoids, Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B [Recombinant] Vaccine was approved by FDA in 2018 for active immunization to prevent diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to Haemophilus influenzae type b. In 2020, FDA approved the first Ebola vaccine (rVSV-ZEBOV vaccine or Recombinant vesicular stomatitis virus-Zaire Ebola virus vaccine) for the prevention of Ebola virus disease caused by Zaire ebolavirus in individuals 18 years of age and older. During the COVID-19 pandemic, in 2020, Pfizer-BioNTech COVID-19 Vaccine was given first emergency use authorization by the FDA and the first emergency use validation from WHO for a vaccine for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2. In 2021, WHO validated AstraZeneca, Janssen, Moderna, COVAXIN, Sinopharm, and Sinovac COVID-19 vaccines for emergency use during the COVID-19 pandemic, while Comirnaty (Pfizer-BioNTech COVID-19 Vaccine) became the first FDA approved vaccine in 2021.

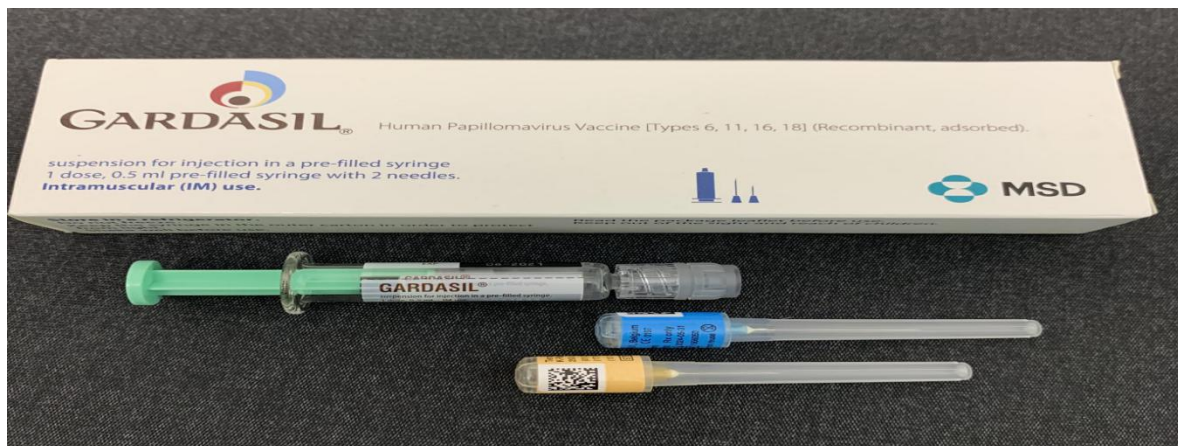


Fig. 39. Gardasil vaccine for Human Papilloma Vaccine (Whispyhistory/CC BY-SA 4.0)

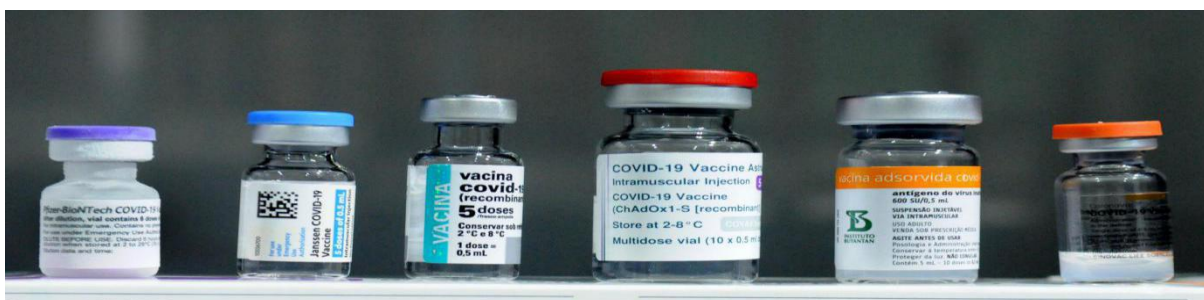


Fig. 40. Different COVID-19 Vaccines (Agência Brasília/CC BY 2.0)

## A Timeline of Major Advances in Medicine During the Last Four Decades

<b>Year</b>	<b>Innovation</b>	<b>Innovator</b>
1980	First commercial MRI scanner (Indomitabe)	Raymond Damadian, Fonar Corporation
1980	Development of a Lithotripter and first treatment of a human with Shock Wave Lithotripsy	Dornier Research Group
1980	Development of the procedure to clone interferons	Sidney Pestka
1980	First implant of Implantable Cardioverter-Defibrillator that is a small battery-powered electrical impulse generator programmed to detect cardiac arrhythmia and correct it by delivering a jolt of electricity	Levi Watkins
1980	First Cochlear Implant in a child	William House
1980	Invention of first Personal Glucose Meter (Dextrometer) for home blood glucose monitoring that allowed people with diabetes to check blood glucose in about one minute	Ames
1980	Pulse Oximeter first marketed in US that provided a noninvasive way to measure a patient's oxygen saturation level	Biox
1981	First Commercial Hepatitis B Vaccine (Heptavax)	Maurice Ralph Hilleman, Merck Pharmaceuticals
1981	Creation of first Artificial skin, a collagen scaffold that induces regeneration of skin, that worked on patients with 50 to 90 percent burns, synthesized as a graft copolymer of microfibrillar type I collagen and a glycosaminoglycan, chondroitin-6-sulfate, fabricated into porous sheets by freeze-drying, and then cross-linked by dehydrothermal treatment	John F. Burke and Ioannis V Yannas
1981	First human heart-lung combined transplant	Bruce Reitz
1981	Invention of Laryngeal Mask Airway, a device that establishes an unobstructed airway in unconscious patients or patients under anesthesia	Archie Brain
1982	Human insulin (Humulin) approved by FDA	Genentech, Eli Lilly and Company
1982	First Artificial Heart Implant	William DeVries
1983	First Surgical Robot "Arthrobot" developed and used	James McEwen and Geof Auchinlek, in collaboration with Brian Day
1983	First DEHP-free and PVC-free Partial Additive Bag PAB	B. Braun
1983	First to Cultivate human keratinocyte stem cells in large quantities for permanent skin restoration	Howard Green
1984	Invention of Stereolithography that laid the basis of first 3d commercial printer	Charles Hull

1984	First genetically engineered mouse model of cancer "oncomouse"	Timothy A Stewart and Philip Leder
1984	Invention and first study on Nicotine patch	Jed Rose, Murray Jarvik, and Daniel Rose
1984	First Radiosurgery using the linear accelerator approach (LINAC) to treat arteriovenous malformation	O. O. Betti, V. E. Derechinsky
1985	NovoPen, the first insulin pen injector launched	Novo Nordisk
1985	First paper published to describe Polymerase chain reaction (PCR) invention	Kary Mullis
1985	First utilization of DNA fingerprinting in a disputed immigration case	Alec Jeffreys
1986	First therapeutic monoclonal antibody approved by FDA (Muromonab-CD3)	Janssen-Cilag
1986	Release of First Automated DNA sequencer (AB370A)	Leroy Hood and Lloyd Smith, introduced by Applied Biosystems.
1986	First recombinant virus-like particle-based vaccine Engerix-B approved in Belgium	SmithKline Biologicals
1986	First selective serotonin-reuptake inhibitors (SSRIs) antidepressant Fluoxetine HCl marketed in Belgium	Ray Fuller, David Wong, and Bryan Molloy from Eli Lilly and Co
1986	Development of First version of DXplain, an Artificial Intelligence decision support system that uses inputted symptoms to generate a differential diagnosis and also serves as an electronic medical textbook, providing detailed descriptions of diseases and additional references	G O Barnett, J J Cimino, J A Hupp, E P Hoffer
1986	Wallstent inserted for the first time into a human coronary artery	Hans Wallstén, Jacques Puel and Ulrich Sigwart
1987	First treatment for HIV (Zidovudine) approved by FDA	Burroughs-Wellcome
1987	Tissue engineering with prospectively design appropriate scaffoldings	Joseph Vacanti & Robert Langer
1987	First tPA (tissue plasminogen activator) Alteplase approved by FDA	Genentech
1987	First commercial digital hearing aid (Nicolet Phoenix)	Nicolet Corporation
1987	First commercially available Statins (Lovastatin)	Merck & Co.
1988	First safety-engineered syringe BD Safety-Lok	Becton Dickinson
1988	Laserphaco Probe patented and utilized for first Laser Cataract Surgery (PhotoAblative Cataract surgery)	Patricia Era Bath
1989	First Pre-implantation Genetic Diagnosis	Alan Handyside
1989	First Living-Donor Liver Transplant	Silvano Raia
1990	Q-switched lasers marketed for scar-free removal of	Derma-lase

	pigmented lesions and tattoos	
1990	Invention of Gamow bag (inflatable bag for treating altitude sickness)	Igor Gamow
1990	Human Genome Project Started	National Human Genome Research Institute, National Institutes of Health
1991	FDA approval of first immunotherapeutic agent (Interleukin 2) for metastatic kidney cancer	Chiron Corporation
1991	Demineralized Bone Matrix Gel	Osteotech Inc
1991	First ventricular assist device (BVS 5000)	Abiomed
1991	First vaccine for hepatitis A (Havrix) approved in Europe	GlaxoSmithKline
1992	Ionic polymer-metal composites superior to previous Electroactive polymers (artificial muscle)	Mohsen Shahinpoor
1992	First augmented reality systems developed with a formally stated objective to enhance human performance during surgery	U.S. Air Force laboratories
1992	first successful birth by Intracytoplasmic sperm injection	Gianpiero Palermo, Paul Devroey and Andre Van Steirteghem
1992	Release of Bioabsorbable Interference Screw	Linvatec Corporation
1992	Functional Magnetic Resonance Imaging - first exploration of regional brain activity using MRI and the BOLD contrast in humans	Kenneth Kwong
1992	First Smart Infusion System (Horizon infusion system)	Kendall McGaw
1993	First Alzheimer's drug Tacrine approved by FDA	William Koopmans Summers
1993	First Photodynamic therapy agent Porfimer sodium approved for clinical use in 1993 to treat a form of bladder cancer in Canada.	Pinnacle Biologics, Inc.
1994	Release of First DNA microarray product (GeneChip)	Stephen Fodor
1994	Palmaz-Schatz Balloon Expandable Stent approved by FDA	Julio Palmaz, Richard Schatz (Johnson & Johnson)
1995	Excimer laser (Exeimed UV200LA and SVS Apex) approved by FDA for Phototherapeutic Keratectomy	Summit Technology Inc
1996	The first mammal cloned from an adult somatic cell (Dolly the sheep)	Keith Campbell, Ian Wilmut and colleagues at the Roslin Institute
1996	Indinavir-based triple-drug therapy for AIDS, HAART (highly active antiretroviral therapy) incorporated into clinical practice that made HIV manageable as a chronic	Hammer and Roy Gulick

	disease	
1996	Release of Bioabsorbable Vascular closure device (Angio-Seal)	Kensey Nash Corp
1996	Medical marijuana legalized for the first time in California	Dennis Robert Peron
1996	First Rapid-cycle PCR with real-time fluorescent monitoring and melting curve analysis (LightCycler)	Idaho Technology Inc.
1997	First FDA approved autologous chondrocyte implantation Product (Carticel)	Genzyme
1997	First occipital craniopagus twins ever separated with both surviving and both being neurologically normal	Ben Carson
1997	First monoclonal antibody for the treatment of a cancer, Rituximab for the treatment of Non-Hodgkin's Lymphoma approved by FDA	Genentech, Inc.
1998	First human embryonic stem cell line	James Alexander Thomson
1998	First FDA approved vaccine for lyme disease (LYMErix)	SmithKline Beecham
1998	First commercial Computer-aided diagnosis CAD system for mammography, the ImageChecker M1000 system approved by the US Food and Drug Administration (FDA)	R2 Technology Inc.
1998	Sildenafil approved for male impotence in the United States and in the European Union	Pfizer
1998	First FDA approved Targeted therapy for HER2-positive metastatic Breast Cancer (Trastuzumab)	Genentech Inc.
1998	A private company started sequencing the human genome and used a different "shot gun" sequencing technique	Craig Venter, Celera Genomics
1999	CyberKnife Robotic Radiosurgery System approved by FDA for treatment of tumors in the head and base of skull	John R. Adler, Russell and Peter Schonberg
1999	Developed a new way to detect nascent cancers with fluorescent molecular probes	Ralph Weissleder and colleagues
1999	First continuous glucose monitor (Continuous Glucose Monitor System) approved by FDA	Medtronic MiniMed
1999	First long-term successful hand transplant	Warren C. Breidenbach, Tsu-Min Tsai from Kleinert Kutz Hand Care Center
2000	First completely robotic surgical system (da Vinci Surgical System) approved by FDA for use in laparoscopic procedures	Intuitive Surgical Inc
2000	World's first quadruple transplant of four organs from a single donor (a kidney, two lungs, and a heart) to four recipients	Brigham and Women's Hospital
2000	Rough draft of the human genome released to the public on the Internet	National Human Genome Research Institute, Celera Genomics
2001	Implant in a human of the first lab-grown organ (a bladder)	Anthony Atala from Wake



	created with a a spatial scaffold	Forest Institute for Regenerative Medicine
2001	First telesurgery (Lindbergh Operation) performed	Jacques Marescaux
2001	Endoscopy capsule approved by FDA	Gabi Iddan and Paul Swai
2002	First rapid HIV test (OraQuick HIV type 1 rapid antibody test) approved by FDA	OraSure Technologies, Inc.
2003	Insulin pump endorsed in the United Kingdom	National Institute for Health and Care Excellence (NICE)
2003	First proteasome inhibitor Bortezomib approved by FDA for use in multiple myeloma	Myogenics and Millennium Pharmaceuticals
2003	First FDA-approved Bluetooth-ready medical device (Stryker integrated device network)	Stryker Corporation
2003	First Organ Transporter (LifePort Kidney Perfusion Transporter) cleared by FDA	Organ Recovery Systems, Inc.
2003	Development of the first Bioprinter	Thomas Boland
2003	First Drug-Eluting Stent (CYPHER™ Sirolimus-Eluting Coronary Stent) approved by FDA	Cordis Corporation, Johnson & Johnson
2003	Human Genome Project successfully completed with completion of draft sequencing of the human genome	National Human Genome Research Institute, National Institutes of Health
2003	Final draft of Human Genome released	National Human Genome Research Institute, Celera Genomics
2004	Development of first Bioprinter that allowed 3D direct biodegradation without the need to build scaffolding.	Gabor Forgacs
2004	First Over-the-Counter Automated External Defibrillator (HeartStart Home Defibrillator) approved by FDA	Philips Medical System
2004	Pinnacle Total Parenteral Nutrition Management System cleared by FDA	B.Braun Medical Inc
2004	First angiogenesis inhibitor Bevacizumab approved by the FDA as a treatment for colon cancer.	Napoleone Ferrara from Genentech
2004	Two studies revealed that immune system senses microbiota under normal conditions and this sensing modulate immune system development under normal conditions leading to the use of Gut microbiota in training the developing immune system and Microbiome therapy	Seth Rakoff-Nahoum and Ruslan Medzhitov
2004	First Natural Orifice Translumenal Endoscopic Surgery (a transgastric appendectomy)	G.V. Rao and D.N. Reddy
2005	First partial face transplant	Jean-Michel Dubernard
2005	First "Enhanced Recovery After Surgery" ERAS protocol for patients undergoing colonic surgery	ERAS Study Group assembled by Ken Fearon and Olle Ljungqvist
2005	Development of an open-style, oxygen mask (OxyMask)	Southmedic Incorporated

2005	First GS20 next-generation DNA sequencer Released	454 Life Sciences
2006	First human papillomavirus vaccine Gardasil approved by FDA	Merck & Co.
2006	The second rotavirus vaccine approved (Previous vaccine withdrawn within 1 year because of its association with intussusception)	Merck
2006	First Lab grown "mini-liver" generated from human cord blood stem cells	Colin McGucklin and Nico Forraz from Newcastle University
2006	As an advancement in Adoptive Cell Transfer (ACT), shown for the first time in humans that administration of normal circulating lymphocytes transduced with a retro-virus encoding a T-cell receptor that recognized the MART-1 melanoma-melanocyte antigen could mediate tumor regression	Richard A Morgan from National Cancer Institute, National Institutes of Health
2006	Conversion of somatic cells into Induced pluripotent stem cells by introduction of four specific genes (Myc, Oct3/4, Sox2 and Klf4)	Shinya Yamanaka
2006	Atripla approved by FDA combining three antiretroviral drugs into one daily pill	Gilead Sciences, Inc
2006	First Dual Energy Source Computed Tomography scanner (Somatom Definition DS) introduced	Siemens Healthcare
2006	The phrase m-Health coined as an abbreviation for mobile health, a term used for the practice of medicine and public health supported by mobile devices	Robert S. H. Istepanian
2006	Launch of Personal Genome Project to correlate genotypes with phenotypes of individuals	George Church
2007	Updates to the Genome published	Craig Venter from Celera Genomics
2007	First commercially available bionic hand (i-LIMB hand)	Touch Bionics
2008	First Low Cost Next Generation Gene Sequencer Polonator G.007 with freely available software and protocols	George Church in partnership with Danaher Corporation and ABI
2008	Impella 2.5 Circulatory Support System cleared by FDA	Abiomed, Inc.
2008	Human Microbiome Project began to study the human as a supraorganism composed of non-human and human cells, with the goal of describing the human microbiome and analyzing its role in human health and disease and to characterize the metagenome of the microbiomes of 300 healthy people, over time	National Human Genome Research Institute, National Institutes of Health
2009	Gene therapy of two 7-year-olds with adrenoleukodystrophy by treating bone marrow cells with a lentiviral vector carrying the gene for the enzyme they lacked apparently arrested the progress of disease	Patrick Aubourg
2009	First commercial 3D bioprinter (NovoGen MMX)	Organovo

2010	First trifocal intraocular lens (FineVision IOL) for cataract surgery launched and implanted that recovers visual acuities at all distances without wearing glasses and solves intermediate vision problems that patients experience with multifocal and bifocal intraocular lens	PhysIOL
2010	First Full face transplant on a man who severely damaged his face in an accident, giving him a new nose, lips, teeth and cheekbones during 24 hours of surgery	Joan Pere Barret from Vall d'Hebron University Hospital
2010	First FDA approved 3D printed orthopaedic implants	Adler Ortho
2010	Senza spinal cord stimulation (SCS) system approved in European Union for chronic pain treatment	Nevro Corp
2010	First cancer vaccine (sipuleucel-T) approved by FDA for castration-resistant prostate cancer	Dendreon Pharmaceuticals
2010	First synthetic cell created	Craig Venter
2011	First 3D bioprinted kidney	Anthony Atala
2011	Nuance Communications and WellPoint partnered with IBM to utilize clinical decision support capabilities of Watson (a Deep QA artificial intelligence supercomputer)	David Ferrucci from IBM
2011	Development of Artificial Intelligence based Phenotyping Technology (Facial Dysmorphology Novel Analysis)	FDNA Inc.
2011	First Implanted Neurostimulation Device obtained CE Mark approval to treat chronic migraine	St. Jude Medical, Inc.
2011	First successful Uterus transplant from a deceased donor	Ömer Özkan and Munire Erman Akar from Akdeniz University Hospital
2011	The first Checkpoint inhibitor anti-cancer drug ipilimumab (a CTLA4 blocker) approved by FDA for the treatment of melanoma	James P. Allison, Medarex, Bristol-Myers Squibb Company
2011	An assistive exoskeleton allowing people with spinal chord injuries to stand upright, walk and climb stairs controlled by a wrist-mounted remote (ReWalk device ) approved by FDA	Argo
2011	Sapien Transcatheter Aortic Heart Valve approved by FDA for Transcatheter aortic valve replacement in patients requiring replacement of aortic valve but not eligible for open-heart surgery	Edwards Lifesciences
2011	Medical mirror invented with an automated face tracker that detects the subtle changes in the blood vessels of the face, every time heart beats, transforming the webcam into a heart-rate monitor	Ming-Zher Poh
2011	First FDA approved targeted therapy for late-stage melanoma that inhibits B-Raf enzyme (Vemurafenib)	Plexxikon and Genentech
2012	Treatment of 17 heart attack patients with cells grown from their own heart tissue resulted in reduced scarring and caused new heart muscle to grow	Eduardo Marbán

2012	First deep convolutional neural network for structure-based drug discovery (AtomNet)	Atomwise, Inc
2012	FDA approved Truvada (Emtricitabine/ Tenofovir) combination pill for use as pre-exposure prophylaxis (PrEP) for HIV, based on growing evidence that the drug was safe and effective at preventing HIV in populations at increased risk of infection	Gilead Sciences, Inc.
2012	Pan-Cancer analysis project launched to assemble coherent, consistent TCGA data sets across tumour types, as well as across platforms, and then to analyze and interpret those data	The Cancer Genome Atlas Research Network (TCGA), National Cancer Institute, National Human Genome Research Institute
2013	First embryonic stem cell made from human skin cells by reprogramming human skin cells back to their embryonic state	Shoukhrat Mitalipov
2013	Antibiotic envelope for preventing infection with cardiac implants (Fully Resorbable AIGISRx R Antibacterial Envelope) cleared by FDA	TYRX, Inc
2013	First bioprinted, bioengineered ears that looks and acts like a natural ear	Jason Spector, Lawrence Bonassar from Cornell University
2013	FDA announced a public meeting entitled "Fecal Microbiota for Transplantation" and regulate human fecal material as a drug	FDA, Els van Nood and various other researchers
2013	First closed loop, brain-responsive neuromodulation system to prevent epileptic seizures (RNS System)	NeuroPace
2013	A prosthetic hand (i-limb ultra revolution) invented that can be controlled via iPhone with the 'bioism' mobile app	Touch Bionics
2013	MitraClip approved by FDA to reduce mitral regurgitation in patients whose significant mitral regurgitation and heart failure symptoms result from abnormalities of the mitral valve and whose risks for mitral valve surgery are prohibitive	Ferolyn Powell, Frederick St Goar, Evalve Inc., Abbott Laboratories
2013	First successful implant of a lab-grown kidney in a rat	Harald Ott
2013	The first human liver grown from stem cells	Takanori Takebe
2013	First Bionic eye Argus® II Retinal Prosthesis System approved by FDA for patients who have no vision or almost no vision due to advanced retinitis pigmentosa.	Mark Humayun, Eugene Dejuan, Howard D. Phillips, Wentai Liu, Robert Greenberg, Alfred E. Mann, Second Sight Medical Products, Inc.,
2013	Sofosbuvir in combination therapy (with a 95% cure rate in combination therapy) approved by FDA for Hepatitis C	Michael Sofia, Pharmasset, Gilead Sciences
2013	A National Institute of Health symposium summarized available evidence of durable (>5 years) weight loss,	National Institute of Diabetes and Digestive and Kidney

	diabetes and lipid improvements with bariatric surgery	Diseases, National Heart, Lung, and Blood Institute
2013	FDA approved Stribild (A combination four HIV medications - cobicistat, elvitegravir, emtricitabine, and tenofovir. into one dose)	Gilead Sciences
2014	Stem cells from adult patients used to generate genetically matched stem cells of each individual.	Young Gie Chung
2014	Development of Pharmabot: A Pediatric Generic Medicine Consultant Chatbot that is designed to prescribe, suggest and give information on generic medicines for children.	Benilda Eleonor V. Comendador
2014	A neuromodulation system for the treatment of heart failure and hypertension (BAROSTIM NEO® System) received CE mark from the National Standards Authority of Ireland (NSAI) to treat heart failure patients with an ejection fraction less than or equal to 35%.	CVRx, Inc.
2014	A Prenatal Screening Blood test for Down syndrome developed	Diana Bianchi
2014	Human embryonic stem cells restored the sight of 18 patients with severe vision loss as a result of two types of macular degeneration	Steven D Schwartz
2014	First 3D printed skull transplant	Bon Verweij
2014	First human clinical trials in the United States for a wearable artificial kidney approved by FDA	Blood Purification Technologies Inc
2014	Inspire Upper Airway Stimulation Therapy for Obstructive Sleep Apnea approved by FDA for use in a subset of patients with moderate to severe Obstructive Sleep Apnea who are unable to use Continuous Positive Airway Pressure	Inspire Medical Systems, Inc.
2014	Mature blood cells from mice reprogrammed into blood-forming hematopoietic stem cells using transcription factors	Derrick J. Rossi, Jonah Riddel
2014	Generation of mature human insulin-producing pancreatic beta cells from stem cells in vitro, which, when transplanted into mice, secrete insulin appropriately in response to glucose levels	Douglas Melton
2014	First successful penis transplant	André van der Merwe, Frank Graewe, Rafique Moosa
2015	Creation of a swatch of tissue containing skin cells interwoven with structural material that can potentially function as blood vessels	Jennifer Lewis
2015	The first 3D printed prescription drug Spritam approved by FDA to treat partial onset seizures, myoclonic seizures and primary generalized tonic-clonic seizures.	Aprecia Pharmaceuticals
2015	Desktop Genome Testing Device, Juno, "The Desktop DNA Lab" developed	Fluidigm Corporation
2015	Development of a microfluidic device to improve early detection and diagnose cancer rapidly at the cellular level	Samir Iqbal, Young-tae Kim, Muhymin Islam

2015	Discovery of Teixobactin, the first new antibiotic in 30 years , that can kill serious infections such as tuberculosis and septicaemia without encountering resistance and could eventually be used to treat drug-resistant infections caused by Methicillin-resistant Staphylococcus aureus	Kim Lewis , NovoBiotic Pharmaceuticals
2015	Discovery of a non-surgical treatment of cataract by using eye drops containing lanosterol or compound 29, that could break away the clumping of proteins in the eye called amyloids that lead to cataracts	Jason Gestwicki, Leah Makley
2015	PCSK9 Inhibitors alirocumab and evolocumab approved by FDA for Cholesterol Reduction	Sanofi, Regeneron, Amgen
2015	Intrastromal Corneal Implantation (KAMRA INLAY) approved by FDA to improve near vision by extending the depth of focus in Phakic, Presbyopic patients	CorneaGen
2016	Development of an automated cognitive assistant for radiologists and cardiologists (Medical Sieve) designed to help in clinical decision-making	Tanveer Mahmood from IBM Syeda
2016	Autologous cultured chondrocytes on porcine collagen membrane MACI (Matrix-induced autologous chondrocyte implantation ) approved by FDA to correct cartilage defects in the knee in adults	Vericel Corporation
2016	First artificial pancreas device system that automatically monitor a person's blood sugar levels and supply insulin when needed. (MiniMed 670G) approved by FDA	Medtronic
2016	First baby born to a mother who was carrying genes for the fatal Leigh syndrome (that affects the DNA in mitochondria) using Mitochondrial replacement therapy	John Zhang
2016	First buprenorphine implant that automatically administer low doses of buprenorphine for the maintenance treatment of opioid addiction (Probuphine) approved by FDA	Titan Pharmaceuticals Inc. and Braeburn Pharmaceuticals
2016	FDA approved Micra transcatheter pacing system (a pill sized single-chamber pacemaker without the need for the wires and leads)	Medtronic
2016	Development of temporary implants and wireless brain sensors that incorporate bioresorbable electronics and materials	John A. Rogers
2016	In a contest by FDA to develop a smartphone app that finds local people with life saving naloxone who can respond when an opiate overdose happens nearby, OD Help became the winning app	PwrdbY
2016	Nusinersen, an RNA-based therapy that contains an antisense oligonucleotide which controls the mutations caused in the chromosome 5q by selectively binding and targeting RNA and regulating gene expression approved by FDA for spinal muscular atrophy	Adrian Krainer, Ravindra Singh, Ionis Pharmaceuticals Inc., Biogen Inc.
2016	Development of Saliva Glucose Biosensor, a pain-free and non-invasive, saliva-based glucose test for diabetes	Paul Dastoor, The iQ Group Global

	management, with a digital healthcare app and a small, disposable strip, which when exposed to an individual's saliva instantly provides a glucose measurement	
2017	Development of 3D-printed breast implants which, dissolve after a year but allows adipose tissue to naturally regenerate	Julien Payen. Lattice Medical
2017	Creation of a 3D printed bioprosthetic ovary that restores ovarian function in sterilized mice	Ramille N. Shah from Northwestern University
2017	First FDA Approved Medical Imaging Analytics Cloud Software With Deep Learning (Arterys Cardio DL) for Cardiac MRI	Arterys, Inc.
2017	First person to receive deep brain stimulation (DBS) for stroke recovery regained motor function	Andre Machado from Cleveland Clinic
2017	Sapien 3 transcatheter heart valve device approved by FDA for transcatheter Mitral Valve replacement	Edwards Lifesciences Corp.
2017	A study showed Ovarian tissue from cancer patients stripped of cells transplanted into mice supported the survival and growth of the follicles giving hope that this could be implanted back into women as artificial ovary and restore their fertility after cancer treatment	Susanne Por from Rigshospitalet
2017	Edaravone approved by the FDA to treat people with amyotrophic lateral sclerosis (ALS)	Mitsubishi Tanabe Pharma Corporation
2017	First Chimeric Antigen Receptor (CAR) T-Cell Therapies approved by FDA Tisagenlecleucel approved for acute lymphoblastic leukemia and Axicabtagene ciloleucel approved for Diffuse Large B-cell lymphoma	Novartis, Kite Pharma, Gilead Sciences, Inc
2017	First Digital smart pills (Abilify MyCite) containing aripiprazole and tiny embedded sensors that track when patients take their medicines and communicate that via smartphone with users approved by FDA	Otsuka Pharmaceutical Co., Ltd
2017	Mandy, a primary care chatbot system created to assist healthcare staffs by automating the patient intake process	Lin Ni, Chenhao Lu, Niu Liu, Jiamou Liu
2017	An AI-enabled Life Coach with an AI chatbot (Wysa) launched for mental and emotional wellness	Touchkin eServices Pvt. Ltd.
2017	Guselkumab approved by FDA for treatment of plaque psoriasis	Janssen Global Service
2017	First in vivo directly administered gene therapy (Voretigene neparvovec) approved by the US Food and Drug Administration (FDA) for the treatment of biallelic RPE65 mutation-associated retinal dystrophy	Spark Therapeutics Inc.
2017	A study showed correction of the heterozygous MYBPC3 mutation (a heritable cardiomyopathy mutation) in human preimplantation embryos using CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)	Shoukhrat Mitalipov
2017	Three targeted cancer therapy drugs approved by FDA for acute myeloid leukemia (midostaurin for FLT3-mutated AML, enasidenib for IDH2-mutated AML, gemtuzumab	Novartis Pharmaceuticals Corporation, Celgene Corporation,

	ozogamicin for CD33-positive AML)	Celltech, Wyeth, Pfizer
2017	Development of smart inhaler by adding add-on sensor to Breezhaler inhalers for COPD treatments	Novartis, Propeller Health
2017	Creation of a non-toxic Surgical super glue from algae that could repair cartilage and patch a hole in the heart of an infant	Jianyu Li
2017	The first breakthrough-designated next generation sequencing based in vitro diagnostic (FoundationOne CDx) approved by FDA to detect a number of different genetic mutations genetic mutations in 324 genes and two genomic signatures in any solid tumor type	Foundation Medicine, Inc.
2017	A cooling cap (DigniCap Cooling System) cleared by FDA for cancer patients with solid tumors to potentially minimize chemotherapy-induced hair loss by constricting blood vessels in the scalp to reduce the amount of chemotherapy that reaches cells in the hair and slowing down cell division in the hair follicles to make them less affected by chemotherapy	Dignitana
2017	First 3D-printed spinal implants (EIT Cellular Titanium Cages) approved by FDA to treat multiple injuries in the spine	EIT Emerging Implant Technologies GmbH
2018	6-in-1 vaccine (VAXELIS) with Diphtheria and Tetanus Toxoids, Acellular Pertussis Vaccine Adsorbed, Inactivated Poliovirus, Haemophilus b Conjugate (Meningococcal Protein Conjugate) and Hepatitis B [Recombinant] Vaccine approved by FDA for active immunization to prevent diphtheria, tetanus, pertussis, poliomyelitis, hepatitis B, and invasive disease due to Haemophilus influenzae type b.	MCM Vaccine Company
2018	First Auricular Reconstruction by in vitro regeneration of Patient-specific Ear-shaped bioprinted Cartilage in five children with unilateral microtia	Guangdong Zhou
2018	First commercial bioprinted human full skin model (Poieskin) made by Laser-Assisted Bioprinting	Poietis
2018	Skin cancer detected more accurately by a deep learning convolutional neural network artificial intelligence system than by dermatologists. Artificial intelligence system that was taught to distinguish malignant moles from benign ones found 95% of melanomas compared to 86.6% for dermatologists	Holger Haenssle
2018	First artificial intelligence medical device to detect diabetic retinopathy in adults who have diabetes (IDx-DR) approved by FDA	IDx LLC
2018	Development of a smartphone-based tool for rapid, portable, and automated wide-field retinal imaging (CellScope Retina)	Tyson N. Kim, Yannis Paulus
2018	First digital inhaler with built in sensors and companion mobile app (ProAir Digihaler) approved by FDA that uses albuterol with sensors to measure inspiratory flow and a Bluetooth chip to view this data in the mobile app	Teva Pharmaceuticals



2018	First FDA approved percutaneous Peripheral Nerve Stimulation Systems SPRINT® endura™ (single lead) and extensa™ (dual lead) for treating chronic and acute pain, including post-operative and post-traumatic pain.	SPR Therapeutics
2018	Development of Cerebrotech Visor System that rapidly detects severe stroke with 92% accuracy through volumetric impedance phase shift spectroscopy	Cerebrotech Medical Systems
2018	Updated ischaemic stroke guidelines released increasing the time window to 16 hours for a selection of acute ischaemic stroke patients and 24 hours for another selection of acute ischaemic stroke patients to receive mechanical thrombectomy when there is large vessel occlusion in the anterior circulation	American Heart Association, American Stroke Association
2018	Development of a liquid biopsy that screens for eight cancer types with a single blood test (CancerSEEK)	Nickolas Papadopoulos, Joshua Cohen Johns Hopkins Kimmel Cancer Center
2018	First in utero stem cell transplantation prior to birth of a woman's stem cells into her growing fetus with alpha thalassemia, leading to the live birth of an infant with a normally fatal fetal condition	Tippi MacKenzie
2018	First genetically edited babies born. CRISPR used to edit embryos germline cells to disrupt the gene for CCR5, a protein on the outer surface of cells that HIV uses to enter to ensure that these babies would be protected from contracting HIV infection	He Jiankui, Michael Deem
2018	First FDA-approved treatment for patients with polyneuropathy caused by hATTR by first FDA approved siRNA (patisiran infusion)	Alnylam Pharmaceuticals, Inc.
2018	Penis transplant with an injection of the bone marrow cells from the donor to speed recovery and prevent rejection	Richard Redett
2018	First successful transplant of lab-grown bioengineered lungs into pigs.	Joan E. Nichols
2018	First 3D printed human corneas	Che Connon, Abigail Isaacson, Steve Swioklo
2018	First implant of PASCAL transcatheter valve repair system in a patient with tricuspid regurgitation	Neil Fam
2019	Development of 3D bioprinted human liver organoids that perform all of the liver's typical functions	Ernesto Goulart
2019	FDA give fast-track designation to regenerative hearing loss treatment drug FX-322. Injecting FX-322 into the middle ear activate progenitor cells to stimulate the regrowth of sensory hair cells in the inner ear to treat sensorineural hearing loss	Frequency Therapeutics
2019	First trial implantation of Orion cortical visual prosthesis system that captures images by a miniature video camera mounted on glasses and converts those into a series of small electrical signals delivered directly to the brain bypassing diseased or injured eyes	Second Sight Medical

2019	Development of waterproof, bandage-like, epidermal, microfluidic sweat sensor with biomarker analysis, and thermography that tells the wearer when to replenish electrolytes and fluids even in aquatic settings	John A. Rogers
2019	First Wearable Peritoneal Dialysis Device that allows dialysis to be performed "on-the-go" granted breakthrough device designation by FDA	AWAK Technologies
2019	Development of a catalogue of the mutational signatures caused by 41 environmental agents linked to cancer	Serena Nik-Zainal, David Phillips
2019	First treatment for episodic cluster headache that reduces the frequency of attacks (Emgality (galcanezumab-gnlm) solution for injection) approved by FDA	Eli Lilly
2019	First Single-Use Duodenoscope, EXALT Model D for use in endoscopic retrograde cholangiopancreatography (ERCP) procedures	Boston Scientific Corporation
2019	An innovative catheter technology Millipede CIS (Clot Ingestion System) that is designed to remove clots from the brain following an acute ischemic stroke granted Breakthrough Device Designation by FDA	Perfuzo
2019	Development of an Artificial Intelligence system that detects lung cancer more accurately than human radiologists. Analyzing a single CT scan, the AI model detected lung cancers 5 percent more often than the experts and was 11 percent more likely to decrease the rate of false positives	Daniel Tse from Google
2019	First 3D-bioprinted bioengineered heart with human tissue, about the size of a rabbit's heart, with cells, blood vessels, ventricles and chambers	Tal Dvir
2019	Trikafta (elexacaftor/ivacaftor/tezacaftor), the first triple combination therapy approved by FDA for patients 12 years and older with cystic fibrosis with the most common cystic fibrosis mutation who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which is estimated to represent 90% of the cystic fibrosis population	Vertex Pharmaceuticals Incorporated
2019	First FDA-approved treatments for Transthyretin amyloid cardiomyopathy (tafamidis meglumine) and (tafamidis)	Pfizer Inc.
2019	First FDA-approved Ebola vaccine (rVSV-ZEBOV vaccine or Recombinant vesicular stomatitis virus-Zaire Ebola virus vaccine) for the prevention of Ebola virus disease caused by Zaire ebolavirus in individuals 18 years of age and older	Merck & Co., Inc.
2019	First drug for osteoporosis that has a dual effect to both increase bone formation and decrease bone resorption (Romosozumab) approved by FDA	Chiroscience, Amgen Inc, Celltech,
2019	A Pivotal Study demonstrated Evoke® Evoked compound action potential-controlled closed-loop stimulation provided significantly greater and more clinically meaningful pain relief up to 12 months compared to open-loop spinal cord stimulation to patients with chronic intractable back and leg	Nagy Mekhail, Saluda Medical

	pain	
2019	First FDA cleared non-drug treatment for ADHD and first medical device to treat attention deficit hyperactivity disorder (ADHD) in 7 to 12 years old pediatric patients who are not currently taking prescription ADHD medication through the use of mild nerve stimulation (Monarch external Trigeminal Nerve Stimulation System or Monarch eTNS System)	NeuroSigma
2020	First liquid biopsy next-generation sequencing companion diagnostic test (Guardant360 CDx assay) approved by FDA to identify patients with specific types of mutations of the epidermal growth factor receptor gene in a deadly form of metastatic non-small cell lung cancer	Guardant Health
2020	Publication of a set of 24 papers analyzing whole genome sequencing and transcriptomic data from 38 tumor types	International Cancer Genome Consortium, TCGA Pan-Cancer Analysis of Whole Genomes project
2020	A study showed that the AI model with DeepMind algorithm could predict breast cancer with the same level of accuracy as a single expert radiologist. Compared to human experts, the system saw a reduction in false positives and in false negatives. AI model performed better than a single radiologist, and was "non inferior" versus two	Google Health
2020	A study reported the successful development and deployment in clinical practice of an AI-based algorithm to accurately detect, grade, and evaluate Prostate Cancer with 98% sensitivity and 97% specificity	Rajiv Dhir, Liron Pantanowitz, Ibex Medical Analytics
2020	A study showed the development of smart contact lenses for both continuous glucose monitoring and treatment of diabetic retinopathy with electrochemical biosensing and on-demand controlled drug delivery. Tear glucose levels of diabetic rabbit models validated by the conventional invasive blood glucose tests	Sei Kwang Hahn
2020	PASCAL transcatheter valve repair system approved by FDA for the treatment of both mitral valve and tricuspid valve	Edwards Lifescience
2020	Palforzia [Peanut (Arachis hypogaea) Allergen Powder-dnfp] approved by FDA to mitigate allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanuts for individuals ages 4 through 17 years with a confirmed diagnosis of peanut allergy	Aimmune Therapeutics
2020	First sodium-glucose co-transporter 2 (SGLT2) inhibitor (dapagliflozin) oral tablets approved by FDA to treat adults with functional class II-IV heart failure with reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization for heart failure	AstraZeneca Pharmaceuticals
2020	First anterior cruciate ligament implant that does not require the use of harvested tendons for ACL repair (Bridge-Enhanced ACL Repair (BEAR) Implant) as an alternative to ACL reconstruction with allograft, autograft	Miach Orthopaedics, Inc.

	or suture-only repair cleared by FDA to treat ACL tears and rupture	
2020	Bempedoic acid approved by FDA for the treatment of adults with heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease who require additional lowering of LDL Cholesterol	Esperion Therapeutics, Inc
2020	Niraparib approved by the FDA as the only oral, once-daily poly ADP-ribose polymerase (PARP) inhibitor monotherapy for first-line maintenance treatment of patients with platinum-responsive advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer regardless of BRCA mutational status	GlaxoSmithKline
2020	First injectable radioactive diagnostic drug for positron emission tomography imaging of prostate-specific membrane antigen positive lesions in men with prostate cancer (Gallium 68 PSMA-11) approved by FDA for assessing patients with suspected prostate cancer metastasis who are potentially curable by surgery or radiation therapy and for patients with suspected prostate cancer recurrence based on elevated serum prostate-specific antigen	University of California
2020	First emergency use authorization by FDA and the first emergency use validation from WHO for a vaccine for the prevention of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (Pfizer-BioNTech COVID-19 Vaccine)	Pfizer Inc.
2021	From 3.5 million cases in 1986 to only 27 in 2020, and only 14 cases from Jan 1 to Nov 30, 2021, Guinea Worm has been 99.99% eradicated from the globe. The introduction of mesh filters and pipe filters for drinking water has Guinea Worm disease poised to be the first parasitic disease to be eradicated, first disease eradicated without vaccines or medications, and the next since smallpox to vanish from the Earth.	The Carter Center, World Health Organization
2021	FDA announced the availability of a final guidance that provides recommendations for nonclinical testing and clinical studies for implanted Brain-Computer Interface (BCI) devices that are neuroprostheses that interface with the central or peripheral nervous system to restore lost motor and/or sensory capabilities in patients with paralysis or amputation.	Center for Devices and Radiological Health
2021	FDA approved first treatment amivantamab-vmjw for adult patients with non-small cell lung cancer whose tumors have epidermal growth factor receptor (EGFR) exon 20 insertion mutations	Janssen Pharmaceutical Companies of Johnson & Johnson
2021	First Extended-Release, Injectable Complete Drug Regimen for HIV-infected adults that is administered once a month (cabotegravir and rilpivirine, injectable formulation) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults approved by FDA	ViiV Healthcare
2021	WHO validated COVISHIELD/AstraZeneca/AZD1222 Oxford vaccines, Janssen, Moderna, Sinovac-CoronaVac,	AstraZeneca, SK Bioscience Co. Ltd, Serum Institute of

	COVAXIN and Sinopharm COVID-19 vaccines for emergency use during the COVID-19 pandemic	India, University of Oxford, Janssen Biotech Inc., Moderna Inc., Sinovac Biotech Ltd, Bharat Biotech China National Pharmaceutical Group Corporation
2021	FDA approved Ephedrine hydrochloride injection for the treatment of clinically important hypotension occurring in the setting of anesthesia	Eton Pharmaceuticals, Inc
2021	FDA granted Breakthrough Therapy designation to 177Lu-PSMA-617, an investigational radioligand therapy for the treatment of metastatic castration-resistant prostate cancer that aims to kill cancer cells in a targeted way while limiting damage to surrounding, healthy cells	Novartis
2021	Semaglutide injection approved by FDA for chronic weight management in adults with obesity or overweight with at least one weight-related condition along with a reduced calorie diet and increased physical activity	Novo Nordisk
2021	First therapy that targets the fundamental pathophysiology of the disease and causes significant reduction of amyloid beta plaque (aducanumab) approved by FDA for the treatment of Alzheimer's	Biogen
2021	Assembled the first truly complete 3.055 billion base pair (bp) sequence of a human genome addressing the previously remaining 8% sequence of the genome, representing the largest improvement to the human reference genome since its initial release	Telomere-to-Telomere Consortium
2021	Development of a neuroprosthetic device that decode words and sentences directly from cortical activity during attempted speech with the use of deep-learning models and a natural-language model in a paralyzed person with anarthria	David A. Moses, Sean L. Metzger, Jessie R. Liu
2021	GI Genius, the first artificial intelligence device to assist clinicians in detecting lesions such as polyps or suspected tumors in the colon during a colonoscopy approved by FDA	Cosmo Artificial Intelligence, Ltd.
2021	FDA approved Cognoa ASD Diagnosis Aid, a machine learning-based device to help diagnose autism spectrum disorder in children 18 months through 5 years of age who exhibit potential symptoms of the disorder	Cognoa, Inc.
2021	Paige Prostate, the first artificial intelligence software designed to identify potential problem areas and assist pathologists in detecting prostate cancer approved by FDA	Paige.AI
2021	FDA approved first drug, Voxzogo (vosoritide) injection to improve growth in children five years of age and older with achondroplasia , the most common form of dwarfism	BioMarin
2021	Vuity (pilocarpine HCl ophthalmic solution 1.25%), first eye drops to treat presbyopia and ending the need of reading glasses in old age approved by FDA	Allergan

2021	FDA approved Adbry (tralokinumab-ldrm), the first treatment specifically targeting IL-13 for adults with moderate-to-severe atopic dermatitis	LEO Pharma
2021	FDA approved Qulipta (atogepant), first oral calcitonin gene-related peptide receptor antagonist specifically developed for the preventive treatment of migraine for the preventive treatment of episodic migraine in adults.	AbbVie
2021	Leqvio (Inclisiran), a twice-yearly injectable siRNA therapy, approved by FDA to Lower LDL cholesterol Levels as an adjunct to diet and maximally tolerated statin therapy in patients with atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia with LDL cholesterol levels that are still too high.	Novartis
2021	First extended-release injectable pre-exposure prophylaxis, Apretude (cabotegravir extended-release injectable suspension) approved by FDA to reduce the risk of sexually acquired HIV in at-risk adults and adolescents	ViiV Healthcare
2021	FDA approved NEUROMARK Rhinitis Neurolysis Therapy , a multi-point nerve disruption treatment for chronic rhinitis that disrupt hyperactive parasympathetic nerves that drive the underlying inflammation	Neurent Medical
2021	FDA approved first COVID-19 vaccine Comirnaty (Pfizer-BioNTech COVID-19 Vaccine) for the prevention of COVID-19 disease in individuals 16 years of age and older. Emergency use authorization granted for individuals 5 years of age and older. Also authorized for use as a heterologous (or "mix and match") single booster dose for individuals 18 years of age and older following completion of primary vaccination with a different available COVID-19 vaccine	Pfizer, BioNTech
2021	FDA's emergency use authorization of long-acting COVID antibody cocktail Evusheld (Tixagevimab/cilgavimab) to protect the immunocompromised before exposure	AstraZeneca
2021	FDA granted emergency use authorization to oral antiviral Covid treatment pills, Paxlovid for patients as young as 12 and, Molnupiravir for adult patients	Pfizer Inc ., Merck & Co's, Ridgeback Biotherapeutics
2021	First patient in the world fitted with a fully digital prosthetic 3D printed eye	Mandeep Sagoo, Moorfields Eye Hospital
2021	FDA granted emergency use authorization to bamlanivimab and etesevimab administered together to treat mild-to moderate COVID-19 or for post-exposure prevention of COVID-19 in adults and pediatric patients including newborn babies who are at high-risk for progressing to severe COVID-19 and/or hospitalization	Eli Lilly
2021	Livtency (maribavir) approved by FDA as the first drug for treating adults and pediatric patients (12 years of age and older) with post-transplant cytomegalovirus (CMV) infection/disease that does not respond to available antiviral treatment for CMV.	Takeda Pharmaceutical Company

## Conclusion

The field of Medicine has advanced at a very fast pace during the last 40 years thanks to the technological and digital revolution. A number of different innovations have taken place during this time period, from inventions of newer types of medicines, innovative surgical procedures, in depth investigative methods and advanced technological devices.

In the 1980's, a number of technological innovations took place including emergence of the first commercial MRI scanner, invention of lithotripter, personal glucose meter, pulse oximeter, cochlear implants and digital hearing aids. There were surgical advancements like the first human heart-lung combined transplant, the first living-donor liver transplant, the first artificial heart transplant, laser cataract surgery, invention of surgical robot, linac radiosurgery and intravascular stent. There was development of newer types of medications like the first SSRI (Fluoxetine HCl), the first treatment for HIV (Zidovudine), first commercially available Statins, invention of Human Insulin, cloning of interferons and the first commercial hepatitis B vaccine. Tissue engineering, polymerase chain reaction (PCR) and automated DNA sequencer were invented and DNA fingerprinting was done for the first time during this decade.

In the 1990s, Human Genome Project began and Dolly, the sheep became the first mammal cloned. There was the invention of the first vaccine for hepatitis A, first vaccine for Lyme disease. Newer treatment modalities began like cancer immunotherapy, targeted cancer therapy and photodynamic therapy. Tacrine was invented as the first drug specifically targeting Alzheimer's and combination drug therapy for HIV (HAART) extended HIV survival. The first human embryonic stem cell line was created and Q-switched lasers, DNA microarray and bionic limbs were invented during this decade. Also, for the first time there was successful separation of type 2 craniopagus twins with both twins staying alive and healthy.

With the turn of the century, the 2000s witnessed the completion of Human Genome Project with completion of draft sequencing of the human genome. First quadruple transplant, first partial face transplant, first full-face transplant, and first telesurgery were also done during this time period. Capsule endoscopy got FDA approval during this decade and there was invention of HPV vaccination. With the increasing use of information technology by doctors and patients and the advent of health supported by mobile devices, the abbreviation mHealth (mobile health) was also coined during this decade.

In 2010s, first successful synthetic cell, first artificial pancreas and first 3D-printed heart using human cells were created. First skull transplant was done. There were inventions like Bionic Eye, Micra Transcatheter Pacing System, and Smart Pills with tiny embedded sensors that communicate via smartphone with users. TAVR (transcatheter aortic valve replacement) for patients who were not eligible for open-heart surgery and eTNS System (external Trigeminal Nerve Stimulation) for treatment of ADHD were given FDA approval. The first cancer vaccine (sipuleucel-T), First Ebola vaccine, the first triple combination therapy for cystic fibrosis mutation (Trikafta) and a new drug called Sofosbuvir with a 95% cure rate for Hepatitis C were FDA approved. There was the discovery of the first new class of antibiotics in 30 years (Teixobactin). Checkpoint inhibitor therapy was invented and first gene therapy and CAR-T cell therapy were given FDA approval. Genome Guided Solid Tumor Diagnosis began and the use of Artificial Intelligence initiated especially in preventative and diagnostic healthcare. In 2020, FDA approved Palforzia to alleviate peanut allergic reactions. During the COVID-19 pandemic, different COVID-19 vaccinations were given FDA or WHO emergency use authorization in 2020 and 2021 including Pfizer-BioNTech, Moderna, Janssen, AstraZeneca,

Sinopharm, Sinovac and COVAXIN, while Comirnaty (Pfizer-BioNTech COVID-19 Vaccine) became the first FDA approved vaccine in 2021.

Advances in medicine during the last 4 decades have played an important role in improving the delivery of health care and the patients' quality of life, with creation of medicines and therapies that have helped millions of people live longer lives. These innovations have opened up possibilities that were previously unimaginable in earlier decades, and have also paved the way for future advancements in medical research and delivery of healthcare.

## References

Ardila, D., Kiraly, A. P., Bharadwaj, S., et al. (2019). End-to-end lung cancer screening with three-dimensional deep learning on low-dose chest computed tomography. *Nature Medicine*, 25(6), 954–961. <https://doi.org/10.1038/s41591-019-0447-x>

Barnett, G. O., Cimino, J. J., Hupp, J. A., et al. (1987). DXplain. An evolving diagnostic decision-support system. *JAMA*, 258(1), 67–74. <https://doi.org/10.1001/jama.258.1.67>

Cartier, N., Hacein-Bey-Abina, S., Bartholomae, C. C., et al. (2009). Hematopoietic stem cell gene therapy with a lentiviral vector in X-linked adrenoleukodystrophy. *Science*, 326(5954), 818–823. <https://doi.org/10.1126/science.1171242>

Chung, Y. G., Eum, J. H., Lee, J. E., et al. (2014). Human Somatic Cell Nuclear Transfer Using Adult Cells. *Cell Stem Cell*, 14(6), 777–780. <https://doi.org/10.1016/j.stem.2014.03.015>

Clark G. M. (2006). The multiple-channel cochlear implant: the interface between sound and the central nervous system for hearing, speech, and language in deaf people—a personal perspective. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 361(1469), 791–810. <https://doi.org/10.1098/rstb.2005.1782>

Comendador, B. E. V., Francisco, B. M. B., Medenilla, J. S. (2015). Pharmabot: A Pediatric Generic Medicine Consultant Chatbot. *Journal of Automation and Control Engineering*, 3(2), 137–140. <https://doi.org/10.12720/joace.3.2.137-140>

Damadian R. (1971). Tumor detection by nuclear magnetic resonance. *Science*, 171(3976), 1151–1153. <https://doi.org/10.1126/science.171.3976.1151>

Fontos G. (2006). Gyógyszerkibocsátó coronariastentek [Drug-eluting coronary stents]. *Orvosi hetilap*, 147(43), 2059–2066.

Foty, R. A., Pflieger, C. M., Forgacs, G., et al. (1996). Surface tensions of embryonic tissues predict their mutual envelopment behavior. *Development (Cambridge, England)*, 122(5), 1611–1620.



Graner, J., Oakes, T. R., French, L. M., & Riedy, G. (2013). Functional MRI in the Investigation of Blast-Related Traumatic Brain Injury. *Frontiers in Neurology*, 4. <https://doi.org/10.3389/fneur.2013.00016>

Haenssle, H. A., Fink, C., Schneiderbauer, R., et al. (2018). Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists. *Annals of Oncology*, 29(8), 1836–1842. <https://doi.org/10.1093/annonc/mdy166>

Isaacson, A., Swioklo, S., Connon, C. J. (2018). 3D bioprinting of a corneal stroma equivalent. *Experimental Eye Research*, 173, 188–193. <https://doi.org/10.1016/j.exer.2018.05.010>

Kucab, J. E., Zou, X., Morganello, S., et al. (2019). A Compendium of Mutational Signatures of Environmental Agents. *Cell*, 177(4), 821-836.e16. <https://doi.org/10.1016/j.cell.2019.03.001>

Kwong, K. K., Belliveau, J. W., Chesler, D. A., et al. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proceedings of the National Academy of Sciences of the United States of America*, 89(12), 5675–5679. <https://doi.org/10.1073/pnas.89.12.5675>

Laronda, M. M., Rutz, A. L., Xiao, S., et al. (2017). A bioprosthetic ovary created using 3D printed microporous scaffolds restores ovarian function in sterilized mice. *Nature Communications*, 8(1), 15261. <https://doi.org/10.1038/ncomms15261>

Lenoir, T., Giannella, E. (2006). The emergence and diffusion of DNA microarray technology. *Journal of biomedical discovery and collaboration*, 1, 11. <https://doi.org/10.1186/1747-5333-1-11>

Lyon, E., Wittwer, C. T. (2009). LightCycler technology in molecular diagnostics. *The Journal of molecular diagnostics : JMD*, 11(2), 93–101. <https://doi.org/10.2353/jmoldx.2009.080094>

Ma, H., Marti-Gutierrez, N., Park, S. W., et al. (2017). Correction of a pathogenic gene mutation in human embryos. *Nature*, 548(7668), 413–419. <https://doi.org/10.1038/nature23305>

Maeda, S., McCandliss, R., Gross, M., et al. (1980). Construction and identification of bacterial plasmids containing nucleotide sequence for human leukocyte interferon. *Proceedings of the National Academy of Sciences of the United States of America*, 77(12), 7010–7013. <https://doi.org/10.1073/pnas.77.12.7010>

Majumdar, A., Kitson, M. T., Roberts, S. K. (2016). Systematic review: current concepts and challenges for the direct-acting antiviral era in hepatitis C cirrhosis. *Alimentary Pharmacology & Therapeutics*, 43(12), 1276–1292. <https://doi.org/10.1111/apt.13633>

McKinney, S. M., Sieniek, M., Godbole, V., et al. (2020). International evaluation of an AI system for breast cancer screening. *Nature*, 577(7788), 89–94. <https://doi.org/10.1038/s41586-019-1799-6>

Mekhail, N., Levy, R. M., Deer, T. R., et al. (2020). Long-term safety and efficacy of closed-loop spinal cord stimulation to treat chronic back and leg pain (Evoke): a double-blind, randomised, controlled trial. *The Lancet Neurology*, 19(2), 123–134. [https://doi.org/10.1016/S1474-4422\(19\)30414-4](https://doi.org/10.1016/S1474-4422(19)30414-4)

Nasser, N. J., Gorenberg, M., Agbarya, A. (2020). First line Immunotherapy for Non-Small Cell Lung Cancer. *Pharmaceuticals*, 13(11), 373. <https://doi.org/10.3390/ph13110373>

Ni, L., Lu, C., Liu, N., et al. (2017). MANDY: Towards a Smart Primary Care Chatbot Application. In *Communications in Computer and Information Science* (Vol. 780, pp. 38–52). Springer. [https://doi.org/10.1007/978-981-10-6989-5\\_4](https://doi.org/10.1007/978-981-10-6989-5_4)

Nickenig, G., Kowalski, M., Hausleiter, J., et al. (2017). Transcatheter Treatment of Severe Tricuspid Regurgitation With the Edge-to-Edge MitraClip Technique. *Circulation*, 135(19), 1802–1814. <https://doi.org/10.1161/circulationaha.116.024848>

Noor, N., Shapira, A., Edri, R., et al. (2019). 3D Printing of Personalized Thick and Perfusible Cardiac Patches and Hearts. *Advanced Science*, 6(11), 1900344. <https://doi.org/10.1002/advs.201900344>

Nurk, S., Koren, S., Rhie, A., et al. (2021). The complete sequence of a human genome. Preprint at BioRxiv. <https://doi.org/10.1101/2021.05.26.445798>

Pagliuca, F. W., Millman, J. R., Gürtler, M., et al. (2014). Generation of Functional Human Pancreatic  $\beta$  Cells In Vitro. *Cell*, 159(2), 428–439. <https://doi.org/10.1016/j.cell.2014.09.040>

Pantanowitz, L., Quiroga-Garza, G. M., Bien, L., et al. (2020). An artificial intelligence algorithm for prostate cancer diagnosis in whole slide images of core needle biopsies: a blinded clinical validation and deployment study. *The Lancet Digital Health*, 2(8), e407–e416. [https://doi.org/10.1016/S2589-7500\(20\)30159-X](https://doi.org/10.1016/S2589-7500(20)30159-X)

Poffo, R., Toschi, A. P., Pope, R. B., et al. (2013). Robotic surgery in Cardiology: a safe and effective procedure. *Einstein*, 11(3), 296–302. <https://doi.org/10.1590/S1679-45082013000300007>

Rao G .V., Reddy D. N. (2006, September). Transgastric appendectomy in humans. Presented at World Congress of Gastroenterology, Montreal, Canada

Reddy, N. and Rao, P. (2004, February). Per Oral Transgastric Endoscopic Appendectomy in Human. Presented at 45th Annual Conference of the Society of Gastrointestinal Endoscopy of India, Jaipur

Reiffel, A. J., Kafka, C., Hernandez, K. A., et al. (2013). High-fidelity tissue engineering of patient-specific auricles for reconstruction of pediatric microtia and other auricular deformities. *PLoS one*, 8(2), e56506. <https://doi.org/10.1371/journal.pone.0056506>

Rex, J., Jensen, K. H., Lawton, S. A. (2006). A Review of 20??Years??? Experience with the Novopen?? Family of Insulin Injection Devices. *Clinical Drug Investigation*, 26(7), 367–401.  
<https://doi.org/10.2165/00044011-200626070-00001>

Riddell, J., Gazit, R., Garrison, B. S., et al. (2014). Reprogramming Committed Murine Blood Cells to Induced Hematopoietic Stem Cells with Defined Factors. *Cell*, 157(3), 549–564.  
<https://doi.org/10.1016/j.cell.2014.04.006>

Rinck, P. A. (2019). *Magnetic resonance in medicine a critical introduction : the basic text book of the European Magnetic Resonance Forum* (12th ed.). Norderstedt Books On Demand.

Roguin, A. (2011). Stent: The Man and Word Behind the Coronary Metal Prosthesis. *Circulation: Cardiovascular Interventions*, 4(2), 206–209. <https://doi.org/10.1161/circinterventions.110.960872>

Saiki, R., Scharf, S., Faloona, F., et al. (1985). Enzymatic amplification of beta-globin genomic sequences and restriction site analysis for diagnosis of sickle cell anemia. *Science*, 230(4732), 1350–1354. <https://doi.org/10.1126/science.2999980>

Schwartz, S. D., Regillo, C. D., Lam, B. L., et al. (2015). Human embryonic stem cell-derived retinal pigment epithelium in patients with age-related macular degeneration and Stargardt's macular dystrophy: follow-up of two open-label phase 1/2 studies. *Lancet (London, England)*, 385(9967), 509–516. [https://doi.org/10.1016/S0140-6736\(14\)61376-3](https://doi.org/10.1016/S0140-6736(14)61376-3)

Serruys, P. W., Strauss, B. H. (1992). The Wallstent Experience: 1986–1990. In *Restenosis after Intervention with New Mechanical Devices* (Vol. 131, pp. 167–189).  
[https://doi.org/10.1007/978-94-011-2650-2\\_10](https://doi.org/10.1007/978-94-011-2650-2_10)

Sigwart, U., Puel, J., Mirkovitch, V., et al. (1987). Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *The New England journal of medicine*, 316(12), 701–706.  
<https://doi.org/10.1056/NEJM198703193161201>

Syeda-Mahmood, T., Walach, E., Beymer, D., et al. (2016). Medical sieve: a cognitive assistant for radiologists and cardiologists. *Medical Imaging 2016: Computer-Aided Diagnosis*, 9785(97850A).  
<https://doi.org/10.1117/12.2217382>

Tachibana, M., Amato, P., Sparman, M., et al. (2013). Human Embryonic Stem Cells Derived by Somatic Cell Nuclear Transfer. *Cell*, 153(6), 1228–1238. <https://doi.org/10.1016/j.cell.2013.05.006>

Takahashi, K., Yamanaka, S. (2006). Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors. *Cell*, 126(4), 663–676.  
<https://doi.org/10.1016/j.cell.2006.07.024>

Thomson, J. A., Itskovitz-Eldor, J., Shapiro, S. S., et al. (1998). Embryonic Stem Cell Lines Derived from Human Blastocysts. *Science*, 282(5391), 1145–1147.  
<https://doi.org/10.1126/science.282.5391.1145>

Wilson, W. C., Jr, Boland, T. (2003). Cell and organ printing 1: protein and cell printers. *The anatomical record. Part A, Discoveries in molecular, cellular, and evolutionary biology*, 272(2), 491–496. <https://doi.org/10.1002/ar.a.10057>

Zhang, B., Gao, L., Ma, L. (2019). 3D Bioprinting: A Novel Avenue for Manufacturing Tissues and Organs. *Engineering*, 5(4), 777–794. <https://doi.org/10.1016/j.eng.2019.03.009>

Zhang, J., Liu, H., Luo, S., et al. (2017). Live birth derived from oocyte spindle transfer to prevent mitochondrial disease. *Reproductive BioMedicine Online*, 34(4), 361–368. <https://doi.org/10.1016/j.rbmo.2017.01.013>

Zhou, G., Jiang, H., Yin, Z., et al. (2018). In Vitro Regeneration of Patient-specific Ear-shaped Cartilage and Its First Clinical Application for Auricular Reconstruction. *EBioMedicine*, 28, 287–302. <https://doi.org/10.1016/j.ebiom.2018.01.011>