SHAKE THE DISEASE

REPORT CROSSTALKS SYMPOSIUM 25.04.2019 - BRUSSELS HEALTH CAMPUS

Imagine your digital twin informing you there's a brain tumor growing under your skull. Imagine the soft and well-targeted arm of an octopus invading your body to remove it, rather than a surgeon's hand holding a scalpel. Imagine augmented reality would make the neurosurgery more visual, intuitive and accurate. Imagine your life, and many more, could be saved by personalized medicine such as gene therapy and immunotherapy. Imagine we could shake the disease in our health care system. Imagine we could convert it to a social network that focuses on health and prevention, rather than sick care. A more patient-centered future is out there, within an arm's reach. Crosstalks put out feelers in three interdisciplinary sessions. (15 min read)

SESSION 1: PERILS & POTENTIALS OF CONNECTED MEDICAL DATA & DEVICES

Or how we must embrace the digital revolution to move from sick care to health care

Marc Noppen (CEO UZBrussels)
'Talking to patients can be a life-saving cure in the digital age'

'Every healthy man is a patient in disguise' are the famous words of Jules Romains, who wrote a satirical play about modern medicine in 1923, *Knock ou le Triomphe de la médecine*. They couldn't be more relevant today to describe our health care system's current state of affairs, said Marc Noppen, CEO of the University Hospital UZ Brussels, opening the session. Health care professionals are too much focused on what's beneficial for them, while maximizing value for patients should be oriented towards achieving the best health outcomes for those who suffer, at the lowest cost. "Our health system needs to evolve to a system that saves health and fosters it. The current sick care approach with the focus on disease is not sustainable in the future. We need to move away from a supply-driven health care system organized around what physicians do toward a patient-centered system organized around what patients need."

"Our Belgian health care system is characterized by a greying population of patients and a huge gap between demand and supply on the health market. Contrary to public conviction, our aging population is particularly suffering from a lifestyle

epidemic, behavioral and chronic diseases like obesities, cardiovascular disease and lung cancer; rather than acute pathologies. Investing in technologies that contribute to the prevention of these illnesses, rather than their treatments, could mean a great step towards cutting costs in our health care systems and make them more efficient and patient-centered.
"In order to find solutions, we need to be creative, and technology can help us with that", said Noppen.

"Technology however is a curse and a threat", he continued. Examples are up for grabs in the news. China's genetically edited babies Lulu and Nana are currently scientists' worst nightmare coming true. The development of drugs for rare diseases (and the way pharmaceutical companies take advantage of this) make our health care system explode. A price tag of 320.000 euros per patient for a new cancer treatment is not fiction, but sadly enough, harsh reality. In our highly networked professional environments, people are overburdened and health workers have become digital zombies.

"Yet technology should not always be regarded as a threat but as part of the solution", is the hospital director's conviction. The information revolution known as Industry 4.0, including cyber-physical interfaces, the Internet of Things, predictive algorithms and automated systems is reaching out to the health care sector indeed, and we should gratefully embrace these technological developments to establish medical aid that prioritizes patients and their health.

At the end of the day, however, good health care is and always will need to be mediated by people. To make his point Noppen referred to the cardiac rehab clinic of the famous Karolinska Institute in Stockholm. Despite huge investments in developing personal apps and wearables for their patients and a top-notch medical platform which allowed for medical follow-up on patients from a distance, the clinic initially was a big failure. It took two smart PhD-students to find out that, after numerous interviews with patients, people felt very uncomfortable with the idea of processing all their medical data themselves. Eventually all it took was more human assistance and a simple phone line to fix the problem. Designing proper, accessible interfaces to make brand new technologies communicate with the human psyche will always remain one of the main challenges. Luckily physicians in times of distress can always draw to a very simple mechanism, Marc Noppen advised, "When everything fails, just talk to your patient".

Koen Kas (Health Care Thinker/Oncologist at UGent)
'By 2030, a digital twin will look after every European citizen's health'

"Two hundred years ago, in China, a doctor was only paid when he succeeded in keeping the local population healthy. Technology can help us with re-establishing a relationship with our health care providers that is focused on prevention and prediction, was the central idea of Koen Kas' talk, health care thinker and visionary. To subsequently bombard the audience with best practices and novel health care experiences from around the globe. Summing up just three of them:

The Peruvian League Against Cancer set up the first, innovative Shadow Wifi System, on Playa Agua Dulce in Peru. The large blue structure lures beach-goers out of the sun with the promise of Wifi: the network is free but it is only available in the shade, providing users with a much-needed break from the sun's potentially harmful rays and educating them about the dangers of skin cancer (excerpt taken from https://smallbusiness.yahoo.com)

The dynamic interior of the Melbourne-based new Medibank (Australia's largest health insurer) focuses on offering employees a healthy and activity-based working environment. To reflect Medibank's values in the vast new space, the focal architectural feature of the building is a series of staircases and ramps connecting the 16 levels, stimulating employees to exercise while working and interacting.

Japan is among the few countries that actively use nursing robots to take care of its aging population. Robear is a nursing-care bear-shaped robot designed to assist elderly Japanese patients in hospitals.

In his capacity of CEO of Healthskouts, a digital platform for the co-creation of medical solutions, Kas wants to contribute to a world "where illness is a thing of the past". Health care providers should find ways to delight their customers and become developers of disruptive solutions by unlocking and connecting medical data silos. AI-based technological devices that are able to crunch and rewire our personal data can support us making the shift from sick care to health care and pave the way towards more personalized medicine and tools assisting us in changing our lifestyles.

Especially genomics and biomarkers will become our guard-

ian angels, Kas believes. Today the human genome, containing approximately 3 billion base pairs of DNA packaged into 23 chromosomes can be sequenced in just 3 hours in return for 200 dollars. "The genomics revolution beats the digital evolution". Referring to Moore's Law, "processing speed of computers is increasing every 18 months", he said. "Genomics is teaching us more about our own biology than we have ever known before. As we learn more about our genomes, said Kas, we can work out how to live better lives. Based on combined individual genetic insights, we can begin to identify people who might be predisposed to certain illnesses, as well as how responsive they are likely to be to certain medication."

Trust is the ultimate key to manage all the medical data we will be digging up by unlocking and connecting our personal digital codes in an ethical, responsible way, Kas continued. He pointed to the Airbnb-network as an example. The global online marketplace and hospitality service that once started as a disruptive technology, soon became extremely successful by establishing trust among complete strangers, thus converting it to an exchange currency that became more worth than money. (*Note from the editors: Although 'trust' should be taken with a pinch of salt here, since in the Airbnb network flats and houses are often rented out by commercial agents, just to make a profit. Apart from the possible lack of security, this has also led to the gentrification of many cities and an increasing social division*).

The pinnacle of technological exploitation of our digital health code is a so-called digital twin, which is being developed as we speak, announced Kas. "In 2019, we are finally able to make virtual copies of ourselves; a digital twin." The oncologist is currently working on an international project funded by EU to build a virtual avatar for every European citizen by 2030, that not only will be wired and trained to think like a health practitioner, but will be able to predict and prevent the 5 most common chronic diseases. Lo and behold a digital doctor to keep us all sane, that won't even have to be paid.

SESSION 2: GENOMICS, GENOME-SCALE TECHNOLOGY & PERSONALIZED THERAPY

Or how breakthrough therapies in precision medicine are facing ethical, social and possibly existential challenges, as our bodies increasingly become hosts for machines.

Marleen Keyaerts (Nuclear Medicine UZ Brussels) and Gil Awada (PhD student UZ Brussels)
'New biomarkers and whole body-imaging techniques can take cancer immunotherapy to the next level'

A ground-breaking, currently extremely challenging technology that is gradually gaining ground in the battle against cancer is cancer immunotherapy. Using components of the human immune system, immunotherapy boosts the body's natural defense mechanisms to fight cancer, as was explained by Marleen Keyaerts and Gil Awada, currently investigating the use of novel biomarkers, in their talk 'From predictive imaging to total body scanners'.

Cancer immunotherapies consist of antibodies that bind to, and inhibit the function of, proteins expressed by cancer cells. Some antibodies attach to specific proteins on cancer cells and flag the cells so the immune system can find and destroy those cells.
Although the treatment still is in an experimental phase, immunotherapy has significantly contributed to the survival of advanced melanoma patients, as was demonstrated with several patient cases. To date, the Food and Drug Administration (FDA) has approved several immune checkpoint inhibitors for the treatment of cancer, such as melanoma and lung cancer.

"Yet, only a subset of patients derive clinical benefit today", said Awada. "In some patients, the disease progresses despite the treatment, other people have displayed toxic responses. It is thus critical to better understand what is exactly driving good response, resistance and possible adverse effects."

"We are currently missing the tools to predict who will and who will not respond to the treatment. Microscopic analysis can tell us something, but won't give us the full picture. The development of more reliable, less invasive biomarkers

would be a great support towards efficient patient selection. Next step forward now is the development of prognostic and predictive biomarkers that can provide better insights into each patient's individual cancer and possible outcomes", added Keyaerts.

Whole body-imaging techniques that can really image the target and provide researchers with more data about the full body of a patient, are future game changers here. "More sophisticated tracers – any type of drug that can be radiolabelled and used as a screening tool to see whether the drug has reached the target – are being improved as we speak and could help us to better understand the disease." Especially nanobodies, a revolutionary biotechnology that was discovered at Vrije Universiteit Brussel in the eighties, show huge potential in this field. "We hope molecular whole body imaging will help improve the prediction of therapeutic efficacy in the future so we can not only spare patients ineffective therapy and potential adverse effects, but also make the treatment more economically appealing, as cancer immunotherapy today is very costly and time intensive."

Thierry VandenDriessche (VUB)
'Nanomolecular surgery at the genetic level is not science fiction anymore, folks!'

Thierry VandenDriessche currently leads the only research group in Belgium that has been focusing on developing gene therapy to pro-actively modify human cells and tissue for over 20 years. "Human life is not the result of a divine intervention, but it's genetic variation that has positioned us humans at the end of evolution since the emergence of primordial soup. Genetic variation makes us what we are today. Generally speaking, we human beings have 200 defects in our genetic code. Luckily, because we are diploid organisms and carry two complete sets of chromosomes, in most cases we have a genetic spare wheel", VandenDriessche set the scene.

"Human DNA is comparable to a full series of Encyclopaedia Britannica, counting 32 volumes and more than 30.000 pages, in which one humble typographic error in some cases however can have far-reaching consequences: One tiny script error can burden us with hereditary transmissible life-threatening disease such as hemophilia", he said.

VandenDriessche has dedicated his academic career to technologically advancing gene therapy for hereditary diseases and cancer following a philosophical-humanistic vision. Refusing to accept that human suffering is predestined by what is written in our DNA, he and his fellow researchers have always fought against dogmatic objection "that a god given body cannot be changed". On the contrary, VandenDriessche stated, it's our moral duty to keep patients from unnecessary suffering, quoting free thinker Baruch Spinoza "Be not astonished at new ideas; for it is well known to you that a thing does not therefore cease to be true because it is not accepted by many".

This pioneering attitude now clearly pays off. Scientists in 2015 successfully applied experimental gene therapy – T cell therapy – to cure the 9 year old Emily Whitehead from cancer in the US, who subsequently became the poster girl of Obama's Precision Medicine Initiative. In 2018 the U.S. Food and Drug Administration approved the first gene therapy to treat cancer and this year long term efficacy has been demonstrated of gene therapy for several diseases. They are "relatively safe, not perfect yet", but good enough to be approved by supranational regulators in Europe and the US.

In Brussels, VandenDriessche especially focuses on treating monogenetic diseases, such as the inherited blood disorder haemophilia, today a death sentence for many patients. His team succeeded to prevent bleeding in a small trial of patients using gene therapy based on attenuated viruses that work as nanomachines to deliver therapy.

Gene therapies work by inactivating or adding a disease-causing gene, or since very recently, since CRISPR/Cas9, the famous molecular scissor for cutting DNA became available, by fixing the mutated broken gene and replacing it by a modified gene. "This allows for nanomolecular surgery at the genetic level", and although still in its infancy, experiments are promising, said VandenDriessche – "It's not science fiction anymore, folks!" As first trials in the States concern non-reproductive cells, ethical concerns are relatively easy to deal with, he said. But the discussion changes entirely when it comes to "tantalizing opportunities" such as modifying embryos, which can pass their genetic alteration on to the next generations, as was the case with the by now notorious Dr. He in China, who intended to genetically reengineer twins to thwart HIV. You then intentionally change homo sapiens, human species.

The ethical compass in drug development and medicine pri-

oritization should always be addressing unmet, high medical needs, was VandenDriessche's conclusion. A widely accepted, validated definition of the term 'unmet medical need' is however urgently required as the technology can easily be exploited to tweak our appearance and boost our physical and intellectual performances. And what about genes that can improve longevity? "Technically, a lot is possible", he confirmed, but the social implications of these procedures are unforeseeable, not to say potentially devastating. There are uncontrollable and non-predictable off-target effects – in nature, there's no such thing as 100 percent reliability. As such, gene therapy is creating a burning platform to conduct further scientific research and extend the ethical debate to the public domain.

ARTISTIC INTERVENTION BY **STELARC** (PERFORMANCE ARTIST)

'This is a time where near dead bodies need not to die'

An unrivalled artist who elevated testing the limits of blending technology with the human body to the utmost personal level is Stelarc, Australian performance artist and Research Fellow at the School of Design and Art at Curtin University in Perth. Since the seventies, Stelarc has been visually probing and acoustically amplifying his body. The extra ear that features as a tiny act in the astonishing list of experiments he has undertaken to explore the stretch between artificial and biological life forms, still sits on his arm, as we could all witness during his talk on the ethical limits of transforming the human body.

"The previous talks clearly illustrated that technology invading the body often still is rather a risk than a solution for pathological conditions" the artist joked, cheerfully opening the session. "We can now preserve dead bodies and preserve them indifferently and at the same time sustain a comatose body by life support systems. We are maintaining dead bodies cytogenetically to reanimate them in some imagined future. This is a time where dead bodies need not to disintegrate and near dead bodies need not to die. The near dead, the brain dead, the yet to be born, the partially living now and synthetic life all share a material and proximal existence with other living organisms, operational machines and executional and viral code."

To name just a few of the ground-breaking endeavours Stelarc presented to the audience: He has used medical instruments, prosthetics, robotics, virtual reality systems, the Internet and biotechnology to engineer intimate and involuntary interfaces with the body. Long before endoscopies became common practice in medicine, he made three films of the inside of his body. He completed 26 body suspension performances with hooks into the skin. He performed with a third hand, an extended arm, a virtual arm, a stomach sculpture and an exoskeleton, a 6-legged walking robot. His *Fractal Flesh, Ping Body* and *Parasite* performances explored involuntary, remote and internet choreography of the body with electric stimulation of the muscles.

Two ideas that are crucial to better understand our current relationship towards technology and serve as mental frame for Stelarc's performances are Bruno Latour's actor-network theory in which a body, machine, virus or algorithm are equally considered as actors with capabilities and qualities that can interact with other actors in systems. Another is Graham Harman's object-oriented ontology, rejecting the idea of human specialness. At the heart of this philosophy is the idea that objects – whether real, fictional, natural, artificial, human or non-human – are mutually autonomous.

"Notions of aliveness need to be interrogated in this age, in this kind of existence. As body implants and prosthetics have become common practice, we are living in a time of circular flesh", Stelarc recited. Doing so, he captured the subject and challenges of current medicine, distinguishing between circular flesh ("We can take organs form one body and insert them into other bodies, transplant cadaver hands on living bodies"), fractal flesh ("Bodies and bits of bodies that are spatially separated, but electronically connected, generating recurring patterns of interactivity at varying scales, in

other words, the Internet") and phantom flesh ("The body now increases itself as its phantom, as its digital double, that can interconnect with other phantom bodies online, where bodies become a kind of digital noise that flickers on and off, a glitch in biological evolutionary time").

"The body itself becomes a host for its machines", Stelarc continued, showing a performance with microbots that invaded his body like "aesthetic gestures towards the increasing intimate relationship of our human body with technology". "With the nanoscaling of technologies, we no longer have to speculate that medical technologies indeed will become invisible. Nanosensors that function as early warning systems to our bodies are truly helpful medical devices."

Reproductive medicine is part of Stelarc's investigative universe as well, giving way to daunting, legitimate ethical questions. "We are now increasingly decoupling our reproductive processes from our daily existences. Frozen embryos that are brought to life as living babies used to be science fiction in a not too distant past, but are considered standard care today: What are the implications of that? Human eggs are viable over several generations. In theory, that means you might be born generations after your mother has passed away. Then human existence begins without birth."

"Increasingly we are coupled with our machines, the body becomes an extended operational system, which is sort of a hybridization of a bodily metabolism with machine musculature, the artist concluded. Consider technological possibilities like artificial wombs and hearts. Now we can 3D print and grow organs from stem cells, there will be a time of organs in excess. Imagine flocks of artificial organs, waiting to be hosted by human bodies, rather than the other way around. If our malfunctioning parts can be replaced increasingly by technological components, technologically, there should be no reason for our bodies to die. How do you define existence that doesn't begin with birth and doesn't end with death? Personally, I think there has always been a ghost in the machine, not as a vital force that animates, but as a fading attestation of the human."

Are artists visionaries who can predict what will happen in the field of science? Stelarc: "Artists generate contestable possibilities, but they are not to be considered as society's early warning systems. Artistic experiments however can pave the way for institutionalized novelties, such as the integration of two human hands in a robotic limb, as the London Brunel University has constructed, and MIT's exoskeleton with additional arms around the waste.

SESSION 3: ROBOTS, AI AND VR & THE TRANSFORMATION OF PATIENT CARE

Or how invasive surgery is integrating top-notch scientific developments on the path to a more patient-centered health care.

Kaspar Althoefer (Queen Mary University of London) 'Next generation surgical robots are based on reverse-engineered animals'

The manipulative abilities of soft-bodied animals have been intriguing engineers for years. Octopuses are boneless animals that can transform their tentacles from a soft state to a stiffness hard enough to catch and even kill prey. Chameleons' tongues unfurl forward faster than a jet plane. Snake-like wavy motion and bending capacities are unrivalled in human engineering.

That is, until very recently. Kaspar Althoefer is conducting research on soft robotics with applications in minimally inva-

sive surgery, assistive technologies and human-robot interaction at Queen Mary University. His research field has seen a dramatic development over the last decade, especially in the field of surgical robots, thanks to animal-inspired behaviours, he said.

"Conventional surgical robots like the robotic da Vinci Surgical System, the world's most advanced surgical robotic system, operate with rigid linked components and can only reach places inside a patient's abdomen by moving along straight lines. They cannot navigate around organs that may be in the way and risk damaging healthy tissue during an operation. Especially in the field of Minimally Invasive Surgery (MIS), tools go through narrow openings and manipulate soft organs that can move, deform, or change stiffness. There are limitations on modern laparoscopic and robot-assisted surgical systems due to restricted access through Trocar ports, lack of haptic feedback, and difficulties with rigid robot tools operating inside a confined space filled with organs."

Replicating the abilities of an octopus tentacle to 'inflate', a snake's capacity to bend around a corner, or a plant that slowly develops new branches out of a sleeve, a new generation of surgical tools is on the rise. The STIFF-FLOP robot (Soft and Stiffness-controllable Robotics Solutions for Minimally Invasive Surgery) for instance is the figurehead of a European funded research project on developing the first generation stiffness controllable robotic instruments for heart and cancer surgery. The innovative soft robotic arm can squeeze through a standard MIS, reconfigure itself and stiffen by hydrostatic actuation to perform compliant force control tasks while facing unexpected situations.

Fijs W.B. van Leeuwen (Leiden University)
'There's huge potential for imaging agents and imaging technologies to advance accuracy in tissue recognition'

Fijs W.B. van Leeuwen, Head of the Interventional Molecular Imaging (IMI) Laboratory at Leiden University took participants yet one level deeper, diving into patients' bodies as he demonstrated what operating a prostate tumor looks like in a video. Operating rooms are hectic places full of people, tools, monitors and infuriating bleeping sounds, as it turned out. Human bodies from the inside look exactly like what human bodies are made of: bones, blood and organ tissue in hundreds of shades of fuzzy pink, in which surgeons must find their ways to the pathologies they need to operate.

The days in which physicians had to rely on Vesalius' drawings of the human anatomy to navigate the human body are, luckily, well behind us. However, although surgeons nowadays can appeal to 3D-imagery to find what they are looking for, identifying the odd body part remains a very tricky thing, van Leeuwen entrusted to the audience. "Even if you have good tools like the da Vinci Surgical System at your disposal, the efficacy of these incredibly expensive surgical robots is still highly debated. In my opinion, for successful surgery a skilled surgeon is and always will be needed to carry out medical procedures. Even then, medicine is an industry: Surgeons too get tired. Errors are being made. There's huge potential for novel technologies to help us out and optimize medical treatments and advance accuracy in tissue recognition."

Van Leeuwen's IMI-group has a high multidisciplinary nature and consists of enthusiastic scientists with a background in biology, medicine, chemistry, nanotechnology, engineering and physics. Jointly they pursue the development of imaging agents and technologies to improve the surgery of, among others, prostate cancer. "Until quite recently, lymphatic mapping (a strategy to trace a tumor) could be compared to pouring a bottle of champagne over a pyramid of glasses. Surgeons were supposed to follow the flow of the liquid to see which glass eventually would fill" – Slash: Find the lymph nodes that were linked to the tumor and had to be removed: A 'crafty', highly ineffective and unreliable approach.

With the upcoming field of image-guided surgery new horizons emerge. New applications are being developed for intra-operative detection of cancerous tissue, using tumor-seeking radiopharmaceuticals. In a similar way, the development of fluorescent tracers gains increasing interest. By combining fluorescent and radioactive tracers, improving imaging systems with augmented and virtual reality and navigation-based robotic surgery, it will be possible to remove tumors entirely and save delicate anatomies surrounding the tumor, Van Leeuwen said. "If we rely on Google Maps-like systems to navigate new neighborhoods, why not physicians to navigate the human body?"

Johnny Duerinck (UZBrussels)
'You may have all the anatomical knowledge in the world but once in there, everything looks the same'.

Johnny Duerinck completed his training in neurosurgery at UZ Brussels, where he has concentrated on (both surgical

and non-surgical) treatment of brain tumors since the beginning of his training. Duerinck conducts research into new treatment methods for brain tumors and also into new technological evolutions in neurosurgery, with an emphasis on implementation of augmented reality into neurosurgery.

"The current limits of the human body that make surgical interventions challenging are fine movements and precise cutting indeed", he endorsed his fellow session speakers, to consequently introduce the concept of neuronavigation. Once entered the body, distinguishing between healthy body tissues and pathologies remains a main challenge, he reaffirmed. "You may have all the anatomical knowledge in the world but once in there, everything looks the same. Human bias, our inclination to keep doing things wrong even when proven wrong, isn't a trustful companion on the journey either. MRI-imagery is often the only reference point to differentiate between brain tissues."

Neuronavigation is the term coined for computer-assisted technologies used by neurosurgeons to navigate in the skull and is in vogue since the nineties, he explained. As surgeons need to rely on different screens and information feeds, they need to continuously shift between mental and physical im-

Acknowledgements to Guy Nagels and Tony Lahoutte of UZBrussels for chairing the sessions.