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March - April 2021

The Syrian PTSD Crisis

10 years of relentless war leaves traumatic mental scars

UAE teen obesity on the rise

Increasing number of young adults undergoing bariatric surgery

A cure for type 2 diabetes?

Long-term study shows bariatric surgery patients stay diabetes-free for 10 years

Anaesthesia mystery

After 175 years, researchers finally figure out how it effects consciousness

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Prognosis

The hidden effects of war

It's been 10 years since the beginning of the war in Syria, making it a good time to again bring to the attention of the world the devastating effects of the war on Syrian civilians. Those who have managed to survive the horror of relentless violence, widespread death and the rampant bombing that has laid waste to their cities across country are now crushed every day by the terrible effects of post-traumatic stress disorder. In this issue we look at a report from the NGO Syria Relief, which places a spotlight on one of the most insidious hidden effects of living in a warzone – post traumatic stress disorder. More than 70% of Syrians who have fled the war-torn country continue to suffer from the traumatic effects of PTSD and in Idlib in Syria 99% of residents are living with the mental scars of PTSD. This eye-opening report gives a face to this hidden crisis and highlights the urgent need for international support to alleviate this humanitarian catastrophe.

And on the subject of the war in Syria, on our new and enhanced website – *www.MiddleEastHealth.com* – we publish a report from the International Committee of the Red Cross, titled: "A Decade of Loss: Syria's Youth After Ten Years of Crisis". It looks in detail at how 10 years of war has robbed an entire generation of Syrians of their younger years.

Also, in this issue, we publish a report from a doctor at Cleveland Clinic Abu Dhabi who is warning that the already high rate of teen obesity in the UAE is, worryingly, continuing to increase as more and more teens are enrolled in their obesity treatment programme. He says the problem needs to be addressed through more community education, as well as the usual recommended behavioural changes to diet and exercise.

Is there a cure for severe diabetes type 2? It seems so, according to a newly published long-term study which shows that diabetes patients who have undergone bariatric surgery have remained diabetes-free for 10-years. The authors of the study say "the evidence is now more than compelling that metabolic surgery should be considered as a main therapeutic option for the treatment of patients with severe type 2 diabetes and obesity".

Take care in this time of the Covid pandemic.

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Update from around the region

Dr. Javed Raza, staff physician and surgeon in the Digestive Disease Institute at Cleveland Clinic Abu Dhabi, says more community education is required to reduce high rate of obesity among teens.

Obesity in UAE teens appears to be increasing

Easy access to high-calorie fast food and fewer physical activity hours are contributing factors to the disturbing rise of overweight and obesity levels among young people in the UAE, say experts at Cleveland Clinic Abu Dhabi.

Patients with a Body Mass Index (BMI) above 25, and with risk factors for chronic diseases, such as diabetes, cardiovascular disease and cancer, are considered for the Obesity Program at Cleveland Clinic Abu Dhabi. Doctors saw an increase in the number of patients seeking medical and surgical treatments for weight loss last year and performed 450 bariatric surgeries in 2020. The program's youngest patients have been between 14 and 18 years of age.

"There's plenty of evidence to suggest that the rates of overweight and obesity in the UAE remain stubbornly high. What is worrying is that these numbers seem to be increasing among young adults," says Dr. Javed Raza, a staff physician and surgeon in the Digestive Disease Institute at Cleveland Clinic Abu Dhabi.

"While the rise in the number of patients is a sign of awareness that they need to get their health back on track, it is also an indication of the scale of the problem, which needs to be addressed through more community education," he says.

According to the Ministry of Health and Prevention, the prevalence of obesity amongst children between the ages of five and 17 in the UAE was 14.45 percent in 2018.

"2020 added the challenge of homeschooling, fewer opportunities for outdoor activities and the convenience of food being delivered at the click of a button. The pandemic may not have caused the high obesity levels, but it did contribute to an unhealthy lifestyle in young people," says Dr. Raza.

Dr. Rahat Ghazanfar, a staff physician in the General Medicine Department in the Medical Subspecialties Institute at Cleveland Clinic Abu Dhabi, says she typically recommends a lifestyle-altering approach for young patients before suggesting a medical or surgical route.

"There are ways to reverse and manage this chronic disease through a good diet and exercise plan. Even if a patient opts for a medical or surgical approach, a complete overhaul of their lifestyle is imperative to make any treatment effective and successful," she says.

Patients of the Obesity Program are cared for by a multidisciplinary team of endocrinologists, metabolic surgeons, nurses, dieticians and patient educators. As part of the program, they are evaluated for comorbidities, hormonal problems associated with obesity, complications and nutritional deficiencies. They are then given a lifestyle, medical, surgical, or a combination plan based on their history, screening and preferences.

Dr. Ghazanfar explains that the care for patients seeking weight loss looks at all aspects of their wellbeing.

"The unique aspect of our program is that we look at all dimensions of health that can be affected by their weight. That includes pulmonology for sleep apnoea, cardiology, psychiatry, advanced endoscopy and gastroenterology to deal with post bariatric problems."

Dr Raza adds that they've enhanced convenience for patients from across the country during the pandemic with more access to ongoing support.

"To make it convenient for our patients, especially those who live in the Northern Emirates, we do regular follow ups virtually through the hospital's health app. We also have a patient support group, which used to meet physically but is now virtual due to the pandemic, for patients who have benefited from the program and want to share their experience and encourage others to take action," he said. MEH

Swiss diagnostics service provider Unilabs expands network in UAE

Unilabs, the leading Swiss diagnostics service provider, has expanded its presence in the UAE by opening a new branch in Abu Dhabi with a testing capacity of up to 80,000 daily PCR tests for Covid-19.

Unilabs provides smart solutions to ensure the safety and efficiency of its tests, while the company's digital communication solutions, especially E-gate which is connected to the Malaffi platform – the UAE's Health Information Exchange – streamlines the laboratory's operations and the delivery of accurate test results.

The opening ceremony was held in the presence of Abdullah bin Mohammed Al Hamed, Chairman of the Department of Health – Abu Dhabi, Mohamed Daoud, CEO, Unilabs Middle East, and several senior officials.

Abdullah bin Mohammed Al Hamed said: "Since the beginning of the Covid-19 pandemic, Abu Dhabi has worked to translate the vision of the UAE's leadership to expand the capacity of Covid-19 testing and ensuring their availability and easy accessibility to all members of the community. The opening of the new branch of Unilabs will contribute to the unwavering efforts towards combating the pandemic."

Daoud commented: "We are extremely proud to be part of the extraordinary efforts made by the UAE's health authorities, whose measures are a global exemplary model in dealing with the pandemic, by expanding laboratory tests for citizens and residents and setting up screening centres for all nationalities to identify and isolate the infected and suspected cases."

"Our expansion plans reaffirm our

commitment to back the efforts of UAE's health authorities in the fight against Covid-19," he said.

The Emirates International Accreditation Centre (EIAC) has granted Unilabs Laboratories the ISO-15189 accreditation, one of the most important international accreditations in the medical laboratory field, for conducting Covid-19 PCR testing in its two branches in Abu Dhabi and Dubai.

Unilab Abu Dhabi is also testing samples collected in other countries and providing the results within 24 hours. With more than 250 laboratories worldwide and some 12,700 employees in 17 countries, Unilabs is considered one of the largest diagnostic providers in Europe. MEH

Kuwait Hospital Sharjah awarded JCI accreditation

The Kuwait Hospital Sharjah, part of the UAE Ministry of Health and Prevention (MoHAP), has been accredited by Joint Commission International (JCI), considered the gold standard in the certification of healthcare quality and patient safety worldwide.

The accreditation was achieved following a comprehensive virtual survey by JCI experts who evaluated the hospital's devices as well as its commitment to applying the best international practices in clinical services, patient safety, and competence of medical and administrative staff, in accordance with the best international standards and protocols.

Abdul Rahman bin Mohammed Al-Owais, the Minister of Health, noted that the ministry is moving forward to have all of its health facilities internationally accredited.

"The rising number of our internationally accredited health facilities is yet another testament to the prestigious position and outstanding level of healthcare services in the UAE," he said

Dr. Youssif Al Serkal, Director-General of the Emirates Health Services Establishment, who attended virtually the procedural process of this accreditation, said, "This accreditation is the result of MoHAP's efforts to apply the unified national standards for hospitals adopted by the UAE Government to achieve best practices in the provision of services, the safety of patients and healthcare providers, hospital design, and health information systems, including medicines, the rights of patients and their families, and the country's linguistic diversity" MEH

NRC Abu Dhabi partners with ITTC network

The National Rehabilitation Centre (NRC) Abu Dhabi, a centre of excellence that collaborates with the World Health Organisation (WHO) in the field of substance abuse in the Middle East, has joined the International Technology Transfer Centre (ITTC) network, making it the only entity from the region to become part of this network.

The network aims to develop the skills of professionals, organisations and systems that provide substance abuse prevention, treatment, rehabilitation, and recovery support services.

The ITTC Network will contribute to implementing the modules included in the training programmes not just in the UAE, but also in the wider region. The network covers South Africa, Ukraine and Vietnam, in addition to a coordination centre in the U.S. The ITTC's scientific group receives support from the International Office of Drug Control and Law Enforcement (INL) of the US State Department, which has a mandate to reduce drug demand, and is associated through a partnership with the International Consortium of Universities on Drug Demand Reduction (ICUDDR).

Commenting on the partnership, Dr Hamad Al Ghafri, Director-General of the NRC, said: "We are proud of the NRC affiliation to the ITTC Network. This is a remarkable milestone for our team in supporting training opportunities, building national technical capabilities, and supporting international collaboration through NRC's partnership with several like-minded organisations in Egypt, Sudan and Seychelles."

He noted that most of the research and technology development in the field of addiction takes place in the US and Europe.

"Our speciality is continuously evolving. Therefore, it is imperative to keep up to date with the recent developments in this rapidly growing field. The nature of this field has led to the development of training that includes evidence-based research such as the Universal Treatment Curriculum (UTC) and the Universal Prevention Curriculum (UPC)," Dr Al Ghafri said. MEH

UAE's MoHAP awarded the Global Conformity Mark for innovation management

The UAE Ministry of Health and Prevention (MoHAP) has been awarded the Global Conformity Mark (GC-Mark) for innovation management.

Following an assessment by a multidisciplinary team of DQS (one of the leading certification bodies for management systems worldwide) and IQNet Association assessors, Dr Youssif Al Serkal, Director-General of the Emirates Health Services Establishment, received the GC-Mark Certificate in the presence of Saqr Alhemeiri, Director of Training & Development Center and Chief Innovation Officer.

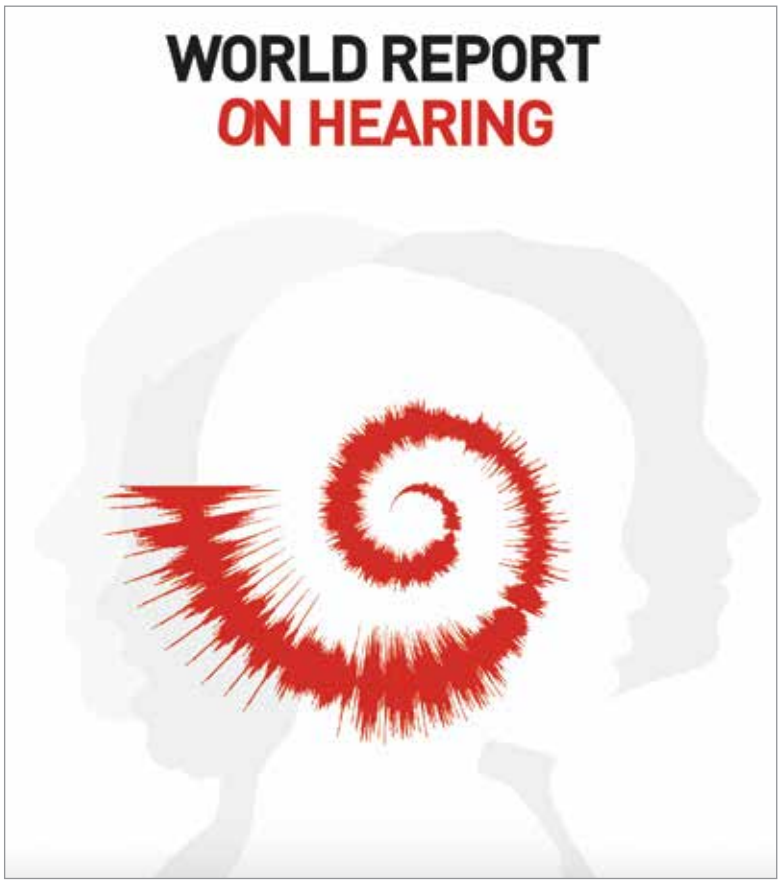
"Obtaining such a prestigious accreditation is testament to the UAE's globally competitive position," said Al-Serkal.

Al-Serkal stressed that the ministry spares no efforts in establishing strategic partnerships with prestigious medical research centres to be ready for future diseases and pandemics, along with the ongoing qualification of national competencies.

He underlined the ministry's keenness to integrate innovative technology into diagnostics and therapeutics by leveraging predictive data and raising preparedness for disease prevention, thus reinforcing the UAE's status as a global innovation hub in the health sector. MEH

worldwide monitor

Update from around the globe



1 in 4 people projected to have hearing problems by 2050

World Report on Hearing calls for expansion of access to ear care

Nearly 2.5 billion people worldwide – or 1 in 4 people – will be living with some degree of hearing loss by 2050, warns the World Health Organization's (WHO) first World Report on Hearing, released March 2, 2021. At least 700 million of these people will require access to ear and hearing care and other rehabilitation services unless action is taken.

"Our ability to hear is precious. Untreated hearing loss can have a devastating impact on people's ability to communicate, to study and to earn a living. It can also impact on people's mental health and their ability to sustain relationships," said Dr Tedros Adhanom Ghebreyesus, WHO Director-General. "This new report outlines the scale of the problem, but also offers solutions in the form of evidence-based interventions that we encourage all countries to integrate into their health systems as part of their journey towards universal health coverage."

The report, launched ahead of World Hearing Day on 3 March, underlines the need to rapidly step up efforts to prevent and address hearing loss by investing and expanding access to ear and hearing care services. Investment in ear and hearing care has been shown to be cost-effective: WHO calculates that governments can expect a return of nearly US$16 for every US$1 invested.

Main findings of the report

Lack of accurate information and stigmatizing attitudes to ear diseases and hearing loss often limit people from accessing care for these conditions. Even among healthcare providers, there's often a shortage of knowledge about prevention, early identification and management of hearing loss and ear diseases, hampering their ability to provide the care required.

In most countries, ear and hearing care is still not integrated into national health systems and accessing care services is challenging for those with ear diseases and hearing loss. Moreover, access to ear and hearing care is poorly measured and documented, and relevant indicators are lacking in the health information system.

But the most glaring gap in health system capacity is in human resources. Among low-income countries, about 78% have fewer than one ear, nose and throat (ENT) specialist per million population; 93% have fewer than one audiologist per million; only 17% have one or more speech therapist per million; and 50% have one or more teacher for the deaf per million. This gap can be closed through integration of ear and hearing care into primary health care through strategies such as task sharing and training, outlined in the report.

Even in countries with relatively high proportions of ear and hearing care professionals, there is unequal distribution of specialists. This not only poses challenges for people in need of care, but also places unreasonable demands on the cadres providing these services.

Main causes of hearing loss

In children, almost 60% of hearing loss can be prevented through measures such as immunization for prevention of rubella and meningitis, improved maternal and neonatal care, and screening for, and early management of, otitis media – inflammatory diseases of the middle ear. In adults, noise control, safe listening

and surveillance of ototoxic medicines together with good ear hygiene can help maintain good hearing and reduce the potential for hearing loss.

Identification is the first step in addressing hearing loss and related ear diseases. Clinical screening at strategic points in life ensure that any loss of hearing and ear diseases can be identified as early as possible.

Recent technological advances, including accurate and easy-to-use tools, can identify ear disease and hearing loss at any age, in clinical or community settings, and with limited training and resources.

Access to timely and appropriate care

Once diagnosed, early intervention is key. Medical and surgical treatment can cure most ear diseases, potentially reversing the associated hearing loss. However, where hearing loss is irreversible, rehabilitation can ensure that those affected avoid the adverse consequences of hearing loss. A range of effective options are available.

Hearing technology, such as hearing aids and cochlear implants, when accompanied by appropriate support services and rehabilitative therapy are effective and cost-effective and can benefit children and adults alike.

The report notes that the use of sign language and other means of sensory substitution such as speech reading are important options for many deaf people; hearing assistive technology and services such as captioning and sign language interpretation can further improve access to communication and education for those with hearing loss.

"To ensure that the benefit of these technological advances and solutions is equitably accessible to all, countries must adopt an integrated people-centred approach," said Dr Bente Mikkelsen, Director of the WHO Department of Noncommunicable Diseases. "Integrating ear and hearing care interventions within national health plans and delivering these through strengthened health systems, as part of universal health coverage, is essential to meet the needs of those at risk of or living with hearing loss."

on the WEB World Report on Hearing
https://www.who.int/publications/i/item/world-report-on-hearing

4 in 10 of world's deaths unregistered – WHO SCORE global report

As many as 4 in 10 of the world's deaths are unregistered and in the African region, a staggering 9 in 10 deaths is currently unrecorded, according to the first ever global assessment of country health information systems provided in the SCORE global report released February 1, 2021 by the World Health Organization in partnership with Bloomberg Philanthropies.

Two-thirds of low-income countries have established a standardized system to report causes of deaths. However, the SCORE global report highlights the urgent need to strengthen these systems to help the world respond to health emergencies and track progress towards global health goals.

The pandemic has highlighted that even the most advanced health and data systems still struggle to provide data in near real-time in order to act swiftly. The lack of data worldwide limits the understanding of the true mortality impact of the COVID-19 pandemic, undermining response planning.

"The pandemic has stretched the capacity of country health information systems around the world, as they must track both the disease and other critical health trends," said Dr Tedros Adhanom Ghebreyesus, WHO Director-General. "The SCORE report is an important step towards better data, for better decisions and better health."

Estimates show that 60% of the countries reviewed have a well-developed system for reviewing progress and performance of their health sector and only half have the capacity to monitor quality of care. Only 32% of the countries have good capacity for a national digital health strategy based on recommended standards.

"With SCORE at hand, WHO will support countries around the world to address data gaps and strengthen their data and health information systems," said Dr Samira Asma, Assistant Director-General, for Data, Analytics and Delivery.

"The SCORE report guides countries to invest in priority areas with the greatest impact on the collection, analysis and use of health data. Among other recommendations the report urges countries to strengthen their overall health data systems, to improve their death data registration systems and to collect more and better quality data to address inequalities," said Michael Bloomberg, WHO Global Ambassador for Noncommunicable Diseases and Injuries.

The SCORE global report report and the portal are part of WHO's SCORE for Health Data Technical Package that will support countries and regions to view their assessments, conduct analyses, and improve health data for healthier populations.

SCORE (Survey, Count, Optimize, Review, Enable) is a technical package of essential interventions, recommended actions, tools and resources that aims to support countries in addressing challenges and meeting health information system needs. It represents – for the first time in a single, harmonized package – all the key elements to enable governments to address data gaps, invest in scalable solutions, and take informed policy action.

- Visit the SCORE dashboard: *https://www.who.int/data/data-collection-tools/score/dashboard#/*

the laboratory

Medical research news from around the world

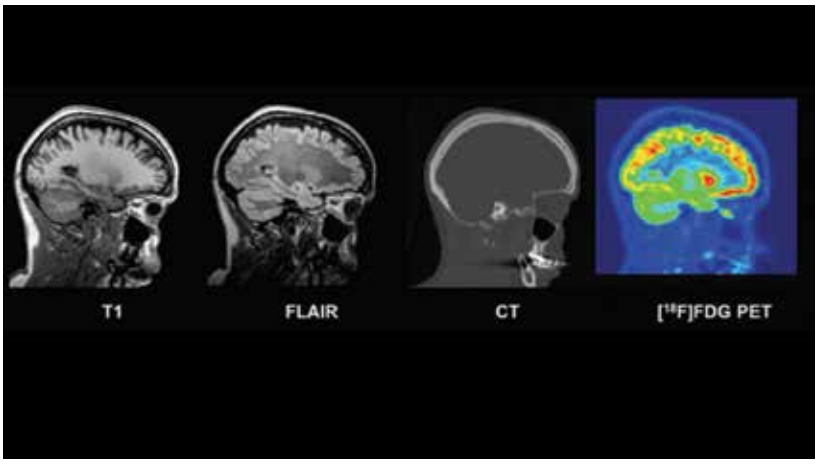


Figure 1: Example of co-registered T1 MRI, FLAIR MRI, CDT and [18F] FDG PET images (sagittal plane) for one subject of the database

New database of healthy adult human brain PET, MRI and CT images is now available for research

A new multi-modal database of healthy adult human brain scans has recently been made available for research.

The acquisition of imaging data can be a costly and logistically difficult process, including gaining participants' consent for acquiring and disseminating their data. The fact that many countries restrict the use of ionising radiation in healthy controls adds to the complexity of neuroimaging research projects. Imaging database sharing plays a key role in the reduction of research costs and radiation exposure.

The CERMEP-IDB-MRXFDG database , a collaboration between King's College London & Guy's and St Thomas' PET Centre at the School of Biomedical Engineering & Imaging Sciences, CERMEP and Neurodis Foundation Lyon, is a collection of PET, CT, and MR images, which allows for quantitative analyses and methodology development in neuroimaging.

Professor Alexander Hammers, Head of PET Centre and one of the senior authors of the study said: "There are quite a few databases of MR images of the brain, but there is very limited choice for brain PET (FDG) databases, especially for younger adults whom we regularly scan with FDG PET/CT as part of their epilepsy surgery workup. Ours is the first I am aware of which is published with the explicit aim of making it available to others."

The age range of subjects – between 23 and 65 - is reflective of participants in research studies at imaging centres on conditions such as epilepsy, movement disorders, multiple sclerosis and disorders of consciousness, allowing statistical comparison to a database of healthy controls.

The database is stored in three different formats: DICOM (data not processed), NIFTI (multimodal images coregistered to PET subject space) and NIFTI normalised (images normalised to the Montreal Neurological Institute (MNI) coordinate system), enabling a high level of interoperability.

The database contains PET images, CT data and two different MR sequences, enabling machine learning of the relationship between modalities and the synthesis of missing modalities. A potential future application is in MR-based attenuation correction for simultaneous PET-MR scanners.

- Interested researchers can request access to the CERMEP-IDB-MRXFDG database via a short form which can be obtained by emailing the lead author, Dr Inés Mérida: *merida@cermep.fr*
- doi: *https://doi.org/10.1101/2020.12.15.422636*

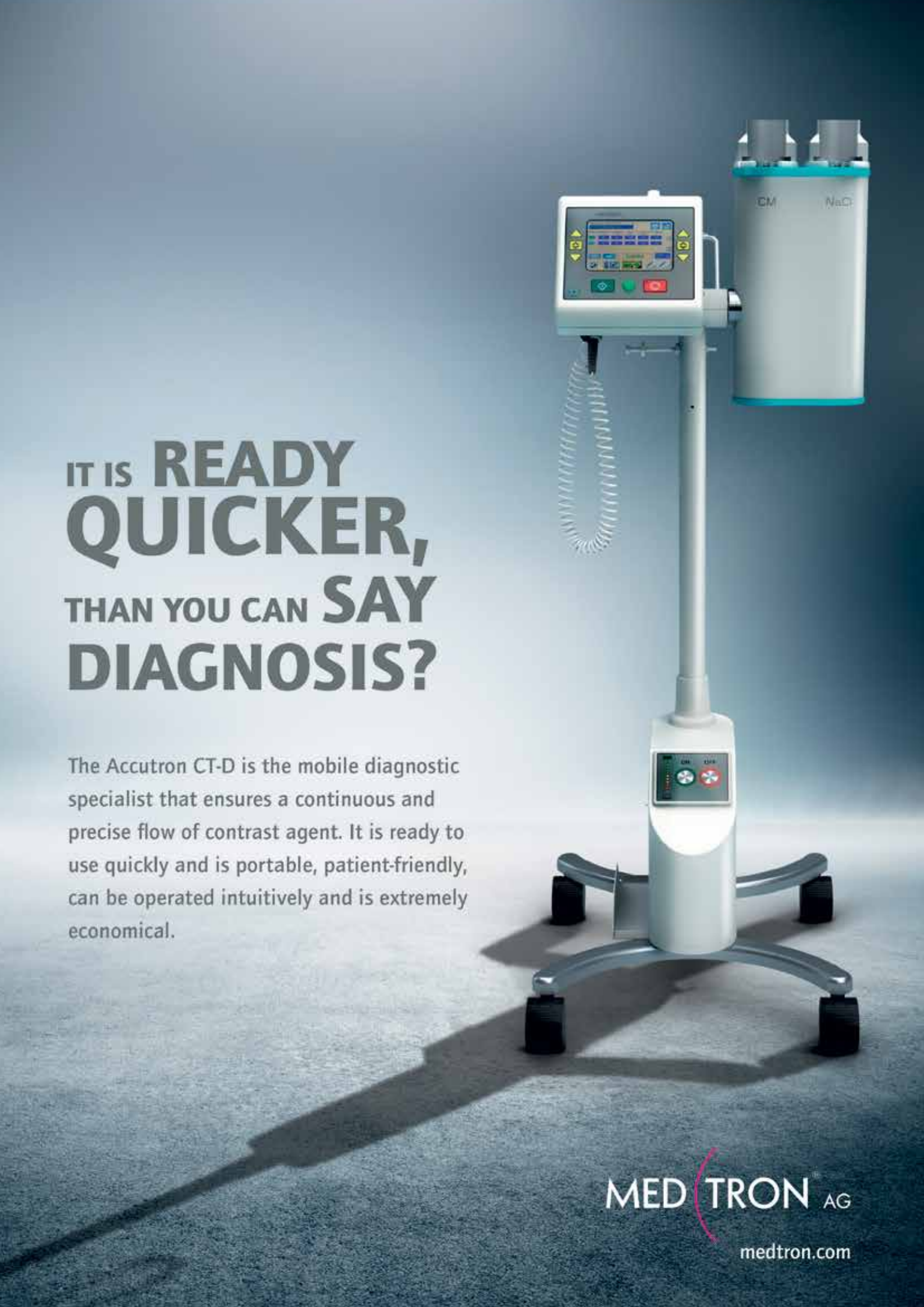
Tuberculosis: New biomarker indicates individual treatment duration

When can tuberculosis therapy be stopped without risk of relapse? Doctors are faced with this question time and again, because the lack of detection of the tuberculosis pathogen Mycobacterium tuberculosis is no guarantee for a permanent cure of the lung infection. Patients who respond to the standard therapy may be out of treatment after six months. But for resistant cases, more than 18 months of treatment duration is currently advised.

"This is a very long time for those affected, who often have to take more than four antibiotics every day and suffer from side effects", explained Prof. Dr. Christoph Lange, Clinical Director at the Research Center Borstel and director of the study, conducted at the German Center for Infection Research (DZIF) in cooperation with the German Center for Lung Research (DZL). "We urgently need a biomarker that enables the implementation of an individualised treatment duration," he emphasises. After all, not every patient needs so long to recover.

Since the absence of bacteria in the sputum does not justify a safe stop in therapy, the team around Christoph Lange set out to find alternative biomarkers in the patient. In collaboration with international tuberculosis centres, on the basis of patient cohorts a model for the end of therapy could be developed that is based on an RNA determination in the blood. From many thousands of genes, 22 have been identified whose activity correlates with the course of the disease.

"The production of RNA of these 22 genes in human blood can tell us whether the patient is cured," PD Dr Jan Heyckendorf from the FZ Borstel said. Together with Maja Reimann and Dr Sebastian Marwitz, he is the lead author of the study. "It is an RNA signature from 22 genes



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identified on two cohorts and validated on another three cohorts," he added. "No other published transcriptom marker shows comparable properties so far."

To identify this individual biomarker, the scientists within the DZIF have established five different patient cohorts. In all cases, these were adults who had contracted pulmonary TB, partly from non-resistant, partly from resistant forms. In addition to cohorts in Germany, patients in Bucharest (Romania) were also included, where the DZIF supports a study centre.

"The individualisation of the treatment duration is an important milestone on the road to precision medicine for tuberculosis," Christoph Lange said. Even without progression values, one could risk to end a patient's treatment on the basis of this RNA determination. As a next step, the researchers are planning a prospective study at the DZIF. The aim is for patients in one study arm to receive treatment for as long as the biomarker suggests, while patients in the other arm receive treatment for as long as the national tuberculosis programme recommends. The scientists then want to see whether the biomarker makes a shorter treatment duration possible. The team around Dr Lange is confident.

"Hopefully, it will then be possible for patients with multidrug-resistant tuberculosis to save about one-third of treatment on average," said Dr Lange.

Reference:
http://dx.doi.org/10.1183/13993003.03492-2020

Digital health tracking tools help individuals lose weight, study finds

Digital health tools, such as diet-tracking apps, increase engagement in weight loss programs, helping users shed pounds, according to a new study.

Weight loss advice is exasperating. Eat breakfast. Don't eat breakfast. No fats. Lots of fats. Run long distances. Exercise hard in spurts.

A new study led by a Stanford Medicine researcher makes at least one thing clear: No matter which weight loss tactic you choose, you're typically more successful if you track your progress with digital health tools.

According to the study, the closer people track their weight-loss efforts with things like smart watches, digital scales and diet-monitoring websites, the more weight they tend to lose.

"We've seen this rise of digital health tools in the last decade, and they provide a great way for people to access interventions to better their health," said Michele Patel, PhD, postdoctoral scholar at the Stanford Prevention Research Center. "We're also starting to see that more weight loss programs are trending toward digital tools, too. But exactly what is being used, how it's being used and the impact it has on the user has never been systematically studied on a large scale."

The analysis also revealed that individuals who tracked their diet or physical activity digitally were more engaged, meaning they were more consistently active in using their digital tools, than those who tracked their behavior through more traditional means, such as handwritten records of exercise routines or calorie intake. In the end, it all comes back to goal-setting and consistency, said Patel, and digital tools can help facilitate both.

A paper detailing the analysis was published online Feb. 24 in *Obesity*.

Digital is convenient

Patel and her team compared nearly 40 different studies on weight-loss monitoring that were conducted between 2009 and 2019. In each study, participants tracked their behaviours, such as calorie and nutrient consumption, the number of daily bites they took and their physical activity, with digital tools. Three-quarters of the time, those who used digital tools more frequently to monitor themselves lost more weight than those who self-monitored less frequently with digital tools, Patel and her colleagues found.

The finding makes sense, Patel said. Tracking allows us to be aware of what we're eating, how much we're moving and how our body weight fluctuates on the scale each day. People can leverage this monitoring feedback to make changes to their daily behaviours. Investigating the grams of nutrients and calories for every meal is burdensome for most people. Digital tools make calorie counting and nutrient tracking easier, she said. Diet-monitoring websites and apps already "know" information about the foods users log – such as the grams of carbs versus fat in a waffle. Some

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apps even allow users to take a picture of their meal and upload it; the app does the rest of the calorie-counting work.

Digital tools may also ramp up engagement by tapping into one's competitive side, as some apps allow for networking or provide visual cues indicating how close one is to reaching a goal – for example, how close one is to completing a colourful circle representing step count.

What's more, the study showed that in-person weight loss coaches weren't necessary for people to stay engaged in weight loss programs. "I think that's promising for individuals who are seeking to lose weight on their own," Patel said.

The other important takeaway, she said, is that it didn't matter what individuals monitored. They could track weight loss, calories or exercise. As long as they did it with digital tools, the more they monitored, the slimmer they became.

Patel plans to dig in deeper to the phenomenon, looking at exactly which behaviour – weight tracking, physical activity tracking, or calorie monitoring – seems to generate the most weight loss. She also plans to specifically recruit people from racial and ethnic minority groups to measure the impact of digital monitoring on weight loss, as these groups are often underrepresented in weight-loss programs.

Deep brain stimulation prevents epileptic seizures in mouse model

Epileptic activity originating from one or more diseased brain regions in the temporal lobe is difficult to contain. Many patients with so-called temporal lobe epilepsy often do not respond to treatment with anti-epileptic drugs, and the affected brain areas must therefore be surgically removed. Unfortunately, this procedure only gives seizure freedom to about one third of patients, so the development of alternative therapeutic approaches is of great importance.

Scientists led by neurobiologist Prof. Dr Carola Haas, head of the research group at the Department of Neurosurgery at Medical Centre, University of Freiburg and the BrainLinks-BrainTools research center, have investigated a new therapeutic approach to prevent epileptic seizures in temporal lobe epilepsy. They showed in mice that low-frequency stimulation of specific brain areas could completely stop epileptic activity. Instead of using electric current, the researchers stimulated the cells with light. To do this, they had previously introduced a light-sensitive molecule into the cells that allows particularly precise stimulation. They published the results in December 2020 in the scientific journal *elife*.

"As soon as we stimulated the brain region with a frequency of one hertz, the epileptic seizures disappeared. This effect was stable over several weeks," Prof. Haas said. Habituation, which can occur with drug therapy, did not take place. The brain region was stimulated for one hour daily.

In temporal lobe epilepsy, the hippocampus is often pathologically altered and usually represents the so-called focus of epileptic activity. Previous studies have used precise genetic labelling techniques to map the fibre system and its synaptic contacts between the temporal lobe and hippocampus, which are typically preserved in temporal lobe epilepsy. The researchers used this fibre system to manipulate hippocampal activity in a specific and temporally precise manner using light-dependent proteins. Measuring brain waves showed that rhythmic activation of the diseased hippocampus at a low frequency of one hertz suppressed epileptic activity and prevented it from spreading.

Haas and her colleagues demonstrated that the anti-epileptic effect is largely due to the repeated activation of surviving granule cells in the seizure focus. Single cell studies confirmed the assumption that the granule cells are less excitable due to the stimulation, making the epileptic seizure less likely to spread.

"It's also possible that we have a widespread network effect because the stimulation can spread through the hippocampal circuitry," Prof. Haas said.

In the future, the team, along with the medical physics department at the Medical Center - University of Freiburg, would like to use magnetic resonance imaging to observe the entire brain during stimulation. This technique could be used to identify additional brain regions that are affected by the stimulation. Corresponding findings on these could provide information on how they are connected and what further consequences stimulation has.

- doi: *https://doi.org/10.7554/eLife.54518*

Massive new genetic sequencing data helps rectify underrepresentation of minority participants in genomic studies

Researchers at the University of Maryland School of Medicine (UMSOM) and their colleagues published a new analysis in the journal *Nature* from genetic sequencing data of more than 53,000 individuals, primarily from minority populations. The early analysis, part of a large-scale program funded by the National Heart, Lung, and Blood Institute, examines one of the largest and most diverse data sets of high-quality whole genome sequencing, which makes up a person's DNA. It provides new genetic insights into heart, lung, blood, and sleep

disorders and how these conditions impact people with diverse racial and ethnic backgrounds, who are often underrepresented in genetic studies.

The program, called Trans-Omics for Precision Medicine (TOPMed), seeks to understand the genetic variations that occur among individuals both in nuclear families and in populations from diverse ethnicities residing on different continents. The project's ultimate goal is to improve the diagnosis, treatment, and prevention of the most common conditions that lead to disability or death.

"We have already identified some surprising new insights," said study corresponding author Timothy O'Connor, PhD, Associate Professor of Medicine & Endocrinology at the Institute for Genome Sciences (IGS) at UMSOM. For example, the team identified more than 400 million genetic variations, but 97 percent of them are extremely rare, occurring in less than one percent of the population.

"Most of the time, these variants mean nothing," said Dr O'Connor, "but they can provide a new understanding of mutational processes and recent human evolutionary history."

The TOPMed team includes more than 180 researchers from leading institutions in genomics worldwide, who have been compiling huge datasets in systematic and defined ways to increase knowledge about diversity in genetic studies. Since its launch in 2014, the TOPMed investigators have begun adding whole genome sequencing and "omics" analysis (which includes a study of genetic and molecular profiles like proteins) to research studies in order to better understand how variations affect different organ systems giving rise to disease in, for example, the heart and lungs.

Causal genetic variants

In the new *Nature* paper, the researchers pointed out that the program "aims to identify causal genetic variants and how they interact with the environment, to characterize disease and its molecular subtypes, to understand differences in disease across diverse ancestries, and to establish a foundation for personalized disease prediction, prevention, diagnosis, and treatment." Braxton Mitchell, PhD, Professor of Medicine at UMSOM, and Jeffrey O'Connell, PhD, Associate Professor of Medicine at UMSOM, were co-authors on this paper.

TOPMed is the largest sequencing project to date and has identified over 400 million gene variants with an overarching mission of understanding global genetic diversity. Since joining the TOPMed program in 2016, UMSOM researchers have published valuable new insights on genetic diversity, including sequencing data from the initial flagship paper on the first 53,831 TOPMed samples.

Increasing diversity

The increasing diversity of the population samples will help investigators learn more about how specific diseases impact different ethnic populations around the world. In addition, the group has established uniform standards for sequencing performed on a massive scale. The standards maximize the integrity of the data as the large group of international researchers use uniform methods as they continue to add other "omics" methods for analysis such as the study of metabolic differences.

"This is a major effort to rectify the

underrepresentation of minority participants in genomic studies and tracks with a broader mission within the School of Medicine to increase diversity in clinical trials," said E. Albert Reece, MD, PhD, MBA, Executive Vice President for Medical Affairs, UM Baltimore, the John Z. and Akiko K. Bowers Distinguished Professor and Dean, University of Maryland School of Medicine. "This hopefully will move the genomics field closer to extending personalized medicine for all patients."

Cashell Jaquish, Ph.D., an NHLBI program officer for TOPMed and a corresponding author on the Nature paper, agrees. "The NHLBI's TOPMed program is a huge resource for the scientific community. We didn't really know what genomic variation looked like in diverse groups until now. This new study represents truly historic findings, and we look forward to continued research studies in this area as we move toward personalized medicine."

In addition to enabling detailed analysis of the combined genomic and health data for sequenced samples, TOPMed has enhanced the analyses of genotyped samples through a new reference panel that now includes over 97,000 individuals. The TOPMed imputation reference panel is publicly available for review and input of new genetic data by researchers.

The first stage of the data release in the Nature study demonstrated a greater inclusion of a diversity of sampling, which will be invaluable to the international group in learning more about the diseases impacting these populations. Because of the vast sample sizes and the longitudinal scope of many of the population samples, the investigators were able to demonstrate that the rare variants represent recent and potentially deleterious changes that can impact protein function, gene expression, or other biologically important elements.

Reference:

Sequencing of 53,831 diverse genomes from the NHLBI TOPMed Program. *Nature*. 10 February 2021. doi: https://doi.org/10.1038/s41586-021-03205-y

A cure for severe diabetes type 2?

Long-term study shows gastrointestinal surgery patients stay diabetes-free for 10 years

The results of a randomized clinical trial with the longest follow up to date show that metabolic surgery is more effective than medications and lifestyle interventions in the long-term control of severe type 2 diabetes.

The study, published January 22, 2021 in *The Lancet*[1], also shows that over one-third of surgically-treated patients remained diabetes-free throughout the 10-year period of the trial. This demonstrates, in the context of the most rigorous type of clinical investigation, that a "cure" for type 2 diabetes can be achieved.

Researchers from King's and the Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy report the 10-year outcomes of a trial that compared metabolic surgery with conventional medical and lifestyle interventions in patients with type 2 diabetes.

The study involved 60 patients with advanced type 2 diabetes and treated at a major academic hospital in Rome, Italy. The patients randomly underwent drugs plus lifestyle interventions or metabolic surgery (gastric bypass or biliopancreatic diversion). At the start of the study, all patients had severe disease, with poorly controlled blood sugar levels and more than five years history of diabetes.

The results of the study show that 37.5% of surgically-treated patients were able to maintain non-diabetic glycaemia without need for diabetes medication – a condition referred to as diabetes remission – for the duration of the 10-year study period. In 2009, American Diabetes Association defined "cure" of diabetes as a continued state of disease remission for more than five years.

Professor Francesco Rubino, senior author of the report and Chair of Bariatric and Metabolic Surgery at King's College London and a consultant surgeon at King's College Hospital in London said: "The findings from this study provide the most robust scientific evidence yet that full-blown type 2 diabetes is a curable disease, not inevitably progressive and irreversible. In addition to represent a major advance in the treatment of diabetes, metabolic surgery is our best lead to the elusive cause of the disease."

Diabetes-related complications

Compared to conventional medical treatment, surgery also resulted in better overall metabolic control, lower cardiovascular risk, better kidney function and quality of life. Notably, patients treated surgically had a significant lower incidence of diabetes-related complications, including cardiac, renal, and neurological adverse events. Metabolic surgery also reduced medication usage, including drugs for diabetes, high blood pressure and dyslipidaemia.

The study investigated the early and long-term safety of the different intervention strategies. Patients who underwent biliopancreatic diversion had more incidences of serious adverse events, including events associated to both disease and intervention, compared to subjects in both other groups. Patients treated by conventional medical therapy had significantly higher incidence of serious adverse events compared to patients who underwent surgery by Roux-en-Y gastric bypass.

Professor Geltrude Mingrone, first author of the report, Professor of Medicine at the Catholic University of Rome and a Professor of Diabetes and Nutrition at King's College London said: "These data corroborate the notion that surgery can be a cost-effective approach to treating type 2 diabetes. The evidence is now more than compelling that metabolic surgery should be considered as a main therapeutic option for the treatment of patients with severe type 2 diabetes and obesity."

> The findings from this study provide the most robust scientific evidence yet that full-blown type 2 diabetes is a curable disease, not inevitably progressive and irreversible.
> – *Professor Francesco Rubino, senior author of the report and Chair of Bariatric and Metabolic Surgery at King's College London*

Previous studies had shown that bariatric or weight loss surgery can induce long-term remission of diabetes in patients with very severe obesity; however, most patients who undergo traditional weight loss surgery have typically mild or recent-onset diabetes. This trial shows the potential curative effect of metabolic surgery for patients with severe disease.

Reference:

[1] Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-centre, randomised controlled trial. *The Lancet*. 23 January 2021. doi: *https://doi.org/10.1016/S0140-6736(20)32649-0*

Antiviral paint for healthcare facilities

Middle East Health speaks to Martin Rosocha, Managing Director at Caparol Arabia about their CapaCare Protect antiviral paint for healthcare facilities.

***Middle East Health*: Can you tell us a bit about CapaCare Protect?**

Martin Rosocha: When the global pandemic hit us last year, our expert solutions team put a lot of effort and worked nonstop to join the fight against Coronavirus. This is the reason why we launched "CapaCare Protect", an innovative and sustainable solution that provides better protection against harmful micro-organisms across the Gulf region. The launch of this product aligns with our company's ethos which is to constantly look for innovative, quality and sustainable solutions to provide comfortable and healthy living. CapaCare Protect is a premium antiviral paint suited for homes, hospitals, clinics and day-care centers.

CapaCare Protect is a premium quality Interior Emulsion developed with SILVERbac technology which uses active silver ions to inhibit the growth of bacteria and viruses on the painted surface which decreases the spread of contagious diseases. It has kill rate of 99.9% against a host of microbes including gram +ve and gram -ve bacteria and virus. This paint enhances indoor comfort as it has zero odor with zero VOC.

The levels of available silver in the paint has been demonstrated to reduce bacterial numbers by greater than 3 logs (99.9% reduction) using a range of American and Japanese International Testing Standards which is considered to have excellent antiviral activity.

Along with viruses and bacteria, CapaCare Protect showed resistance to mould and fungus as well contamination which would allow reduced cleaning to be undertaken and any related complications in the healthcare environment which would lead to respiratory illness do to mould spores released into the air form contaminated walls in areas of damp.

***MEH*: How did you carry out testing of the product?**

MR: CapaCare Protect is the only paint in the region that has shown 99.9% kill rate against the coronavirus. Tests were conducted according to American and Japanese standards in two independent ISO 17025 laboratories in the United States and were approved and accredited by International Antimicrobial Council (IAC).

***MEH*: How is CapaCare being applied in the region, and for which sectors is it the most suitable and advantageous?**

MR: CapaCare Protect is manufactured in our production plant in the UAE and has already been significantly used on various projects including hospitals, commercial, residential areas and schools. We received solid demand from the market for this product which is on the rise and its production is expected to continue growing.

CapaCare Protect is washable, easy to clean and maintain and is highly recommended for hospitals, schools, malls, restaurants and all living spaces. For instance, it has been approved for DAFZA (Dubai Airport Free Zone authority), Gems School, Saudi German Hospital, Dubai London Hospital, Rashid Center of Disability, Sofitel JBR and many other high-profile projects across the Middle East.

***MEH*: Can you tell us about your future plans in the Middle East?**

MR: We want to play a key role in supporting the positive development of the region and reflect governmental transition towards a green economy. We are seeing positive shifts in the market with more and more developers keen to make projects more efficient and sustainable. There's a real opportunity to help them improve the performance and safety of their buildings and enhance the experience of residents with our innovative solutions.

Martin Rosocha, Managing Director at Caparol Arabia

As a green company, we also want to continue championing indoor air quality and offer our VOC-free paints which can be complementary to a healthier lifestyle and play a central role in the protection of our environment and well-being. Our motto is: "Everyone should be living and working in healthy, well-designed, efficient and sustainably constructed buildings."

On a regional level, we are also planning to expand our innovative products to tailor to the demand of the market. MEH

Damage to the heart found in more than half of Covid-19 patients discharged from hospital

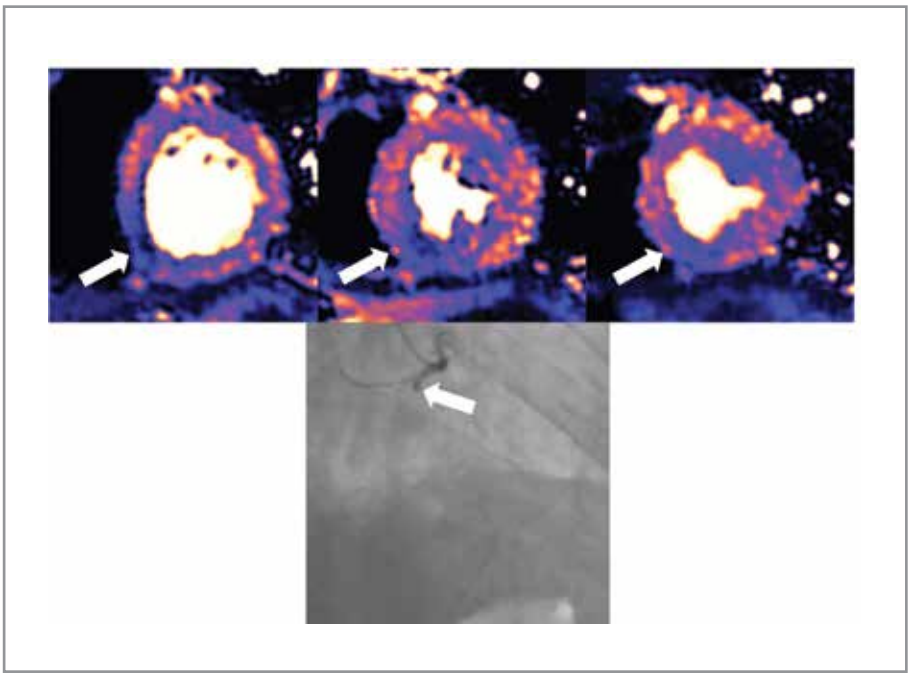
The European Society of Cardiology is reporting that around 50% of patients who have been hospitalised with severe Covid-19 and who show raised levels of a protein called troponin have damage to their hearts. The injury was detected by magnetic resonance imaging (MRI) scans at least a month after discharge, according to new findings published in the *European Heart Journal* [1].

Damage includes inflammation of the heart muscle (myocarditis), scarring or death of heart tissue (infarction), restricted blood supply to the heart (ischaemia) and combinations of all three.

The study of 148 patients from six acute hospitals in London is the largest study to date to investigate convalescing Covid-19 patients who had raised troponin levels indicating a possible problem with the heart.

Troponin is released into the blood when the heart muscle is injured. Raised levels can occur when an artery becomes blocked or there is inflammation of the heart. Many patients who are hospitalised with Covid-19 have raised troponin levels during the critical illness phase, when the body mounts an exaggerated immune response to the infection. Troponin levels were elevated in all the patients in this study who were then followed up with MRI scans of the heart after discharge in order to understand the causes and extent of the damage.

Professor Marianna Fontana, professor of cardiology at University College London (UK), who led the research with Dr Graham Cole, a consultant cardiologist at Imperial College London, said: "Raised troponin levels are associated with worse outcomes in Covid-19 patients. Patients with severe Covid-19 disease often have pre-existing heart-related health problems including diabetes, raised blood pressure and obesity. During severe Covid-19 infection, however, the heart may also be directly affected. Unpicking how the heart can become damaged is difficult, but MRI scans of the heart can identify different patterns of injury, which may enable us to make more accurate diagnoses and to target treatments more effectively."



MRI scan of damaged heart. Blue means reduced blood flow, orange is good blood flow. In this figure the inferior part of the heart shows dark blue, so the myocardial blood flow is very reduced and the black and white angiography, which looks directly at the blood vessels, shows that the vessel which supplies the blood to this part of the heart is occluded. The 3 coloured images are 3 different slices of the heart: the basal the mid and the apical slice.

The researchers investigated Covid-19 patients discharged up until June 2020 from six hospitals across three NHS London trusts: Royal Free London NHS Foundation Trust, Imperial College Healthcare NHS Trust and University College London Hospital NHS Foundation Trust. Patients who had abnormal troponin levels were offered an MRI scan of the heart after discharge and were compared with those from a control group of patients who had not had Covid-19, as well as from 40 healthy volunteers.

"The recovering Covid-19 patients had been very ill; all required hospitalisation and all had troponin elevation, with around one in three having been on a ventilator in the intensive care unit," said Prof. Fontana.

"We found evidence of high rates of heart muscle injury that could be seen on the scans a month or two after discharge. Whilst some of this may have been pre-existing, MRI scanning shows that some were new, and likely caused by Covid-19. Importantly, the pattern of damage to the heart was variable, suggesting that the heart is at risk of different types of injury. While we detected only a small amount of ongoing injury, we saw injury to the heart that was present even when the heart's pumping function was not impaired and might not have been picked up by other techniques. In the most severe cases, there are concerns that this injury may increase the risks of heart failure in the

future, but more work is needed to investigate this further."

The function of the heart's left ventricle, the chamber that is responsible for pumping oxygenated blood to all parts of the body, was normal in 89% of the 148 patients but scarring or injury to the heart muscle was present in 80 patients (54%). The pattern of tissue scarring or injury originated from inflammation in 39 patients (26%), ischaemic heart disease, which includes infarction or ischaemia, in 32 patients (22%), or both in nine patients (6%). Twelve patients (8%) appeared to have ongoing heart inflammation.

Prof. Fontana said: "Injury relating to inflammation and scarring of the heart is common in Covid-19 patients with troponin elevation discharged from hospital, but is of limited extent and has little consequence for the heart's function.

"These findings give us two opportunities: firstly, to find ways of preventing the injury in the first place, and from some of the patterns we have seen, blood clotting may be playing a role, for which we have potential treatments. Secondly, detecting the consequences of injury during convalescence may identify subjects who would benefit from specific supporting drug treatments to protect heart function over time."

The findings of the study are limited by the nature of patient selection and included only those who survived a coronavirus infection that required hospital admission.

"The convalescent patients in this study had severe Covid-19 disease and our results say nothing about what happens to people who are not hospitalised with Covid, or those who are hospitalised but without elevated troponin. The findings indicate potential ways to identify patients at higher or lower risk and suggest potential strategies that may improve outcomes. More work is needed, and MRI scans of the heart have shown how useful it is in investigating patients with troponin elevation," concluded Prof. Fontana.

Reference

[1] "Patterns of myocardial injury in recovered troponin-positive Covid-19 patients assessed by cardiovascular magnetic resonance", by Tushar Kotecha et al. *European Heart Journal*.
doi: *https://doi.org/10.1093/eurheartj/ehab075*

Study shows asthmatics have no higher risk of dying from Covid

A new study looking at how Covid-19 affects people with asthma provides reassurance that having the condition doesn't increase the risk of severe illness or death from the virus.

George Institute for Global Health researchers in Australia analysed data from 57 studies with an overall sample size of 587,280. Almost 350,000 people in the pool had been infected with Covid-19 from Asia, Europe, and North and South America and found they had similar proportions of asthma to the general population.

The results, published in the peer-reviewed *Journal of Asthma*, show that just over seven in every 100 people who tested positive for Covid-19 also had asthma, compared to just over eight in 100 in the general population having the condition. They also showed that people with asthma had a 14 percent lower risk of acquiring Covid-19 and were significantly less likely to be hospitalized with the virus.

There was no apparent difference in the risk of death from Covid-19 in people with asthma compared to those without.

Head of The Institute's Respiratory Program, co-author Professor Christine Jenkins said that while the reasons for these findings weren't clear, there were some possible explanations - such as some inhalers perhaps limiting the virus' ability to attach to the lungs.

"Chemical receptors in the lungs that the virus binds to are less active in people with a particular type of asthma and some studies suggest that inhaled corticosteroids - commonly used to treat asthma - can reduce their activity even further," she said.

"Also, initial uncertainty about the impact of asthma on Covid-19 may have caused anxiety among patients and caregivers leading them to be more vigilant about preventing infection."

Lead author Dr Anthony Sunjaya added that while this study provides some reassurance about the risks of exposure to Covid-19 in people with asthma, doctors and researchers were still learning about the effects of the virus.

"While we showed that people with asthma do not seem to have a higher risk of infection with Covid-19 compared to those without asthma and have similar outcomes, we need further research to better understand how the virus affects those with asthma," he said.

When the Covid-19 pandemic first spread across the world concerns were raised that people with asthma might be at a higher risk of becoming infected, or of becoming sicker or even dying.

Previous findings have shown that people with chronic respiratory conditions like asthma were reported to be at greater risk during the Middle East Respiratory Syndrome (MERS) outbreak, caused by a virus with a similar structure.

"Respiratory infections like those caused by coronaviruses can exacerbate asthma symptoms and corticosteroid treatment may increase susceptibility to Covid-19 infection and its severity," Dr Sunjaya said.

However this study using the best evidence available on the risk of infection, severe illness – requiring admission to ICU and/or ventilator use – and death from Covid-19 in people with asthma finds "no significant difference" of people with asthma being at higher risk.

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Lab study suggests blood group A poses higher risk for Covid-19 infection

As researchers around the world work to identify and address risk factors for severe Covid-19, there is additional evidence that certain blood types could be associated with greater risk of contracting the disease. A new *Blood Advances* study details one of the first laboratory studies to suggest that SARS-CoV-2, the virus that causes Covid-19, is particularly attracted to the blood group A antigen found on respiratory cells.

In the study, researchers assessed a protein on the surface of the SARS-CoV-2 virus called the receptor binding domain, or RBD. The RBD is the part of the virus that attaches to the host cells, so it is an important research target for understanding how infection occurs. The team assessed synthetic blood group antigens on respiratory and red blood cells found in blood group A, B, and O individuals, and analysed how the SARS-CoV-2 RBD interacted with each unique blood type. They discovered that the RBD had a strong preference for binding to blood group A found on respiratory cells. It did not display a preference for blood group A red blood cells, or other blood groups found on respiratory or red cells. The capacity of the RBD to preferentially recognize and attach to the blood type A antigen found in the lungs of blood type A individuals may provide insight into the potential link between blood group A and Covid-19 infection.

"It is interesting that the viral RBD only really prefers the type of blood group A antigens that are on respiratory cells, which are presumably how the virus is entering most patients and infecting them," said study author Sean R. Stowell, MD, PhD, of Brigham and Women's Hospital. "Blood type is a challenge because it is inherited and not something we can change. But if we can better understand how the virus interacts with blood groups in people, we may be able to find new medicines or methods of prevention."

Based on their observations, the team sought to determine whether a similar binding preference existed for the RBD of SARS-CoV, the virus that causes severe acute respiratory syndrome (SARS). Although the makeup of the virus differs, the SARS-CoV RBD exhibited the same preference to bind to the group A antigens on respiratory cells.

Dr Stowell and his team emphasized that their findings alone could not fully describe or predict how coronaviruses like SARS-CoV-2 and SARS-CoV would affect patients of various blood types. "Our observation is not the only mechanism responsible for what we are seeing clinically, but it could explain some of the influence of blood type on Covid-19 infection."

While further research is needed to understand that influence, the paper adds to findings from earlier *Blood Advances* studies suggesting a possible link between blood type and Covid-19 susceptibility and severity. MEH

Covid-19 infection in pregnancy not linked with still birth or baby death

Covid-19 infection in pregnancy is not associated with stillbirth or early neonatal death, according to a new study.

However the research, from over 4000 pregnant women with suspected or confirmed Covid-19, also found women who had a positive test were more likely to have a premature birth.

The research, led by scientists from Imperial College London and published in the journal Ultrasound in Obstetrics and Gynecology, used data from the UK and the USA.

The study team looked at data from 4004 pregnant women who had suspected or confirmed Covid-19. Of these women, 1606 were from the UK, from a data registry called PAN-Covid, while 2398 were from the US, from the American Academy of Pediatrics SONPM data registry.

PAN-Covid was funded by the Medical Research Council, UK National Institute for Health Research and the NIHR Imperial Biomedical Research Centre.

All the women gave birth between January-August 2020.

The research found that no babies died from Covid-19 in the study. There was also no increase in risk of stillbirth or low birth weight.

However, both the UK and US data suggested a higher risk of pre-term birth (defined as birth before 37 weeks).

In the UK data, 12 per cent of women with suspected or confirmed Covid-19 had a pre-term delivery – 60 per cent higher than the national average rate of 7.5 per cent. In the US data, 15.7 per cent of women had a pre-term birth, 57 per cent higher than the US national average of 10 per cent.

The study team say part of this association may be due to doctors deciding to deliver the baby early due to concerns about the effect of Covid-19 infection on mother and baby. The rate of spontaneous pre-term birth was lower than expected.

Professor Christoph Lees, senior author of the study from Imperial's Department of Metabolism, Digestion and Reproduction, said: "The finding that Covid-19 infection does not increase the risk of stillbirth or baby death is reassuring. However, a suspected or confirmed Covid-19 diagnosis was linked to a higher risk of preterm birth, and it isn't entirely clear why."

Dr Ed Mullins, co-author from Imperial's Department of Metabolism, Digestion and Reproduction, added: "This study supports the prioritisation of vaccination for women who are pregnant or who plan to become pregnant, and existing measures that protect women in pregnancy from infection, in order to reduce pre-term birth." MEH

Australian respirator manufacturer finds itself at forefront of COVID-19 crisis

CleanSpace Technology, an Australian company that designs and manufactures next-generation respirators, has found itself at the forefront of the COVID-19 pandemic.

The proprietary technology, at the heart of all CleanSpace Respirators, was designed by ex-ResMed biomedical engineers. ResMed is a world leader in CPAP devices. The engineers had a vision to make respirators that delivered high level protection in an easy to use and comfortable system. The company has been successfully protecting workers in a wide range of sectors for the past ten years.

Until CleanSpace, the technology for masks had not changed for 30 years. Traditional devices were typically uncomfortable, hot and provided low protection.

"Our technology was seen as game-changer, and still is. One of the main reasons people go unprotected is because of low compliance. If masks are uncomfortable or not quick and easy to put on then it simply doesn't get used," said Alex Birrell, CleanSpace Technology CEO. "CleanSpace is unique, it's a Powered Air Purifying Respirator (PAPR) without the heavy and cumbersome belt and hoses associated with PAPRs. Its simplicity with fresh air on the face, makes it far preferable to the N95 disposable [mask]."

The clear silicon mask is comfortable and soft and allows for easy communication. CleanSpace Respirators are operated using a simple one-button smart system. These features combined mean healthcare workers are more likely to wear them for a full shift.

Compared to disposable masks, CleanSpace Respirators offer more protection and are more economical as the cost of replacing disposables stacks up. Disposable masks are well-known for causing fogging and discomfort, leading to low compliance.

CleanSpace HALO

Following the Ebola outbreak in 2014, the WHO and CDC put out a call for light weight highly protective PAPRs specifically designed for healthcare workers. CleanSpace Technology were confident, with their medical device background and a commercially proven technology, they could develop a healthcare respirator. Thirty percent lighter, smaller and more ergonomic than its predecessors, CleanSpace HALO was the first respirator to be designed in consultation with healthcare.

Well before the COVID-19 crisis, CleanSpace HALO was protecting the lives of thousands of frontline healthcare workers globally. Since the outbreak, this unique system has become the 'standard of care' for protection of high-risk healthcare teams in anaesthetics, surgery and general care. The advantages of reusable systems with superior protection and a secure supply chain make this Australian manufacturer an attractive and reliable vendor for many Australian and international hospitals.

Since COVID-19, with the rapid depletion of disposable masks and reliance on lean supply chains, hospitals were suddenly desperately seeking alternatives to disposable masks.

"The need is very real and very urgent, we have had to quickly adapt our manufacturing to respond to the need," added Dr Birrell.

CleanSpace HALO is designed specifically for the healthcare, pharmaceutical and laboratory sectors and are being used to protect the lives of thousands of frontline healthcare workers globally.

Smart technology for respiratory protection

CleanSpace HALO is a PAPR system that houses smart technology in a revolutionary, compact design. CleanSpace delivers the highest protection in healthcare while being comfortable, quick to fit and easily integrated into any setting.

- High Protection P3/TM3 99.95%
- Reusable and cost-effective
- Lightweight 400g/0.9lb
- No belts or hoses
- Simple and fast to put on
- IP rated 66 water tolerant
- More information: *https://cleanspacetechnology.com/health/*

CleanSpace STERI-PLUS exhalation filter for source control

The world's first PAPR exhalation valve filter is utilised for source control in sterile settings where filtering of the wearer's exhaled air is required.

- Filtration efficiency 99% for particles 0.3µm and above
- Approved for use with CleanSpace respirators & CleanSpace half masks
- Reusable case is compatible with standard disinfection/sterilization protocols
- Easy to fit. Easy to clean
- Cost-Effective
- Learn more:

Flyer: *https://cleanspacetechnology.com/health/resources/*

Video: *https://cleanspacetechnology.com/health/steri-plus-exhalation-filter/*

CleanSpace Technology, an Australian company based in Sydney, assists in product training, fit testing and instructions on maintenance and care with attentive customer support.

- Contact CleanSpace Technology to request a demonstration

sales@cleanspacetechnology.com
www.cleanspacetechnology.com

Maintaining safe IV infusion therapy during the COVID-19 pandemic

Smart pumps with Dose Error Reduction Systems (DERS) reduce the risk of medication error, but the requirement for strict isolation of large numbers of patients during the COVID-19 pandemic has made maintaining the *Rights* of IV medication administration increasingly difficult.

Right Maintenance of continuous critical short half-life infusions (CSHLI), such as Noradrenaline or Glyceryl Trinitrate is also vital as any prolonged interruption of CSHLI delivery could be fatal, and nursing staff must respond promptly to any infusion alarm if serious cardiovascular events are to be avoided. Centralised monitoring of infusions can significantly reduce nurse reaction times to CSHLI alarms.

To reduce nursing time inside SARS-CoV-2 patient rooms we can use long extension lines that allow the patient's pumps to remain outside of the isolation room. Running the IV line under the door and across the room's floor, with taping to prevent tripping or dislodgment, is not ideal but provides protection of the line. However, the technique may cause issues of pressure gradient changes affecting occlusion alarms, and accumulation of air in the line due to the low level of the line in relation to the pump and the patient.

Long lines increase siphonage in the case of large bore lines and increase downstream pressure when microbore lines are used. It is important to maintain the recommended height of the infusion bag above a large volume pump (this is usually 50 centimetres) and any unnecessary resistance in the downstream line should be reduced by limiting the number of extension-set additions whilst achieving a safe working distance, and infusing through as large an IV catheter as possible. Priming of long extension lines can be undertaken by gravity, but it is often easier to control the prime by using the pump. Downstream occlusion pressure limits may need to be increased to avoid nuisance alarms, particularly at higher rates with narrow tubing. This can be done by bedside-users, but with wireless-connected smart pumps changes to default pressure alarms configurations can be made centrally and distributed rapidly via the network to all pumps.

Studies on the cleaning of long-lines and their materials suggest that wiping a PVC extension set 2-3 times daily with 70% isopropyl alcohol solution has minimal impact on the line's function and performance (i.e. there will be no weakening leading to excess kinking or excessive compliance in the line). It is therefore expected that PVC IV extension sets would still deliver their critical function with minimal risk to clinician or patient.

For intermittent infusions nurses should consider priming long extension-sets with the medication rather than with normal-saline or dextrose, to facilitate prompt delivery. Post-medication flushes should be given at the same rate as the medication, the pump's 'restore' function can help achieve this.

Appropriate cleaning and decontamination of pumps between patients, and on a regular basis, is a both vital component of pandemic planning, as well as being central to any 'standard' infection control plan. Selection of infusion pumps is a factor here. There should be no difficult to access areas that can harbour contaminant and that cannot be exposed to disinfectant material. This includes plunger grips on syringe pumps and line or cartridge loading spaces on large volume pumps. Furthermore, the pump's body must be not be degraded by cleaning products that can fight SARS-CoV-2. New polymers released in the last few years by some pump manufacturers have considerably broadened the cleaning products that can be used without fear of damage to the device.

Becton Dickinson

Article supplied by Clinical Resource Consultants, Medication Management Solutions, Eastern Europe, Middle East & Africa. Becton Dickinson.

Greiner Bio-One

Glucose stabilisation right from the beginning

VACUETTE FC Mix Tube from Greiner Bio-One provides effective glycolysis inhibition for precise determination of in vivo blood sugar content

Plasma glucose levels are essential for the evaluation of diabetes mellitus as well as gestational diabetes. Diabetes mellitus is one of the most common metabolic disorders in the world. The breakdown of glucose (glycolysis) in venous blood samples is of great significance in pre-analytics, particularly in relation to the diagnosis of diabetes mellitus and gestational diabetes.

Greiner Bio-One has a solution in the form of the VACUETTE® FC Mix Tube. This special additive mixture not only reduces the pH value and blocks the pH-dependent enzymes that would be active in the initial stage of the glycolysis cascade. The VACUETTE FC Mix Tube from Greiner Bio-One can also stabilise the sample immediately after collection for up to 48 hours.

The time from collection until separation of plasma and cells, temperature as well as cell count strongly affect glucose levels possibly leading to false low results. Unfortunately, fluoride alone is not able to stabilise the real in-vivo glucose level completely.

VACUETTE FC Mix Tubes are citrated and therefore can help to prevent the initial loss of glucose within the first few hours from collection until fluoride shows its effect. Buffered Na2EDTA, citric acid, sodium citrate and sodium fluoride are used to decrease the pH and block the pH dependent enzymes, which would be active in the initial stage of the glycolysis cascade.

The shatter-proof tube is made of polyethylene terephthalate (PET). PET is important for the stability of the vacuum. The safety cap is particularly easy to open and allows for hygienic working. The transparent plastic label provides an optimum view of the tube contents.

The powder additive in the VACUETTE FC Mix Tube has no dilution effect. There is no need to take a conversion factor into consideration. Inverting ten times ensures that the tube additive is completely dissolved and well mixed with the sample.

Should the tubes be stored longer than 24 hours at room temperature, samples should be centrifuged after blood collection. Centrifuged aliquots from FC Mix Tubes can be stored for up to 48 hours at room temperature. Tubes should be centrifuged within 20 minutes after blood collection. Cooling of the samples is also suitable for 48 hours glucose stabilisation.

- For more information, *visit: www.gbo.com*

ICRC

A young Syrian refugee in the Ruwaishid area, Jordan.

The Syrian PTSD crisis

Syria Relief, one of the world's leading Syria-focused NGOs, has published research which shows that 74% of Syrian refugees in Lebanon and 76% of Syrian refugees in Turkey have Post-Traumatic Stress Disorder (PTSD) symptoms. In war-torn Idlib, Northwest Syria, 99% of Internally Displaced Persons (IDPs) have symptoms of PTSD.

Syria Relief is labelling this "the Syrian PTSD crisis".

Charles Lawley, the author of the report and Syria Relief's Head of Communications and Advocacy, says: "This report finally quantifies and gives a face to the Syrian PTSD crisis that many of us working with the victims of the Syrian conflict have long suspected. However, the results are worse than what we feared."

Othman Moqbel, Chief Executive Syria Relief, notes in the report: "Whilst the world concentrates its attention towards fighting the COVID-19 pandemic, Syrians are gripped by a mental health epidemic which the world is ignoring, just like many of the aspects of this decade-long conflict. Syria Relief, like many NGOs working inside Syria and the neighbouring countries, receive donor support to provide aid to treat the symptoms of the damage that you can see – food, water, education and physical health projects – but there is not currently the same will from donors to deal with this spiralling mental health crisis."

Lawley adds: "We are hoping that now we can finally measure the impact of trauma on the victims of conflict, the aid community will be better supported to provide the psychosocial support that is clearly needed. We also hope that mental health first aid and a holistic response to conflict and crises can be taken and the psychological needs are also provided for.

"This conflict has touched every Syrian in some way. Our fear is that this will be the legacy of this conflict, when the bombs and guns eventually fall silent. For Syrian people, the mental scars will continue bleeding long after the physical ones have healed."

Moqbel says in the report that "refugees and IDPs may have escaped the conflict physically, but PTSD means many will be unable to truly escape this conflict, even when the brutal fighting finally ceases, unless their condition is treated".

"This report does not just prove that this unseen crisis exists with empirical evidence, but it gives it a face. I hope the numbers you see and the stories you read will work towards generating more international support to alleviate the humanitarian catastrophe that we can't see – mental health amongst the victims of this decade of inhumanity."

The destruction you can't see

The report, The Destruction You Can't See: A report into the prevalence of PTSD symptoms amongst IDPs and refugees from the Syrian conflict, finds:

- 88% of the 721 respondents from different locations in Idlib, Syria, Beqa'a Valley, Lebanon and Istanbul, Hatay, Ga-

ziantep and Kilis, Turkey have symptoms compatible with PTSD

- All but 2 of the 393 respondents (IDPs) in Idlib (99%) have PTSD symptoms
- 76% of respondents in Turkey and 74% in Lebanon (refugees) have PTSD symptoms
- Of the 15 possible symptoms, 42% of people have experienced at least one life threatening event and have 10 or more PTSD symptoms (37% in Idlib, 50% in Lebanon, 52% in Turkey) and 84% have 7 or more symptoms (88% in Idlib, 73% in Lebanon, 80% in Turkey)
- When it comes to analysing what percentage of people believe that there is mental health support available to them, refugees in Turkey report to have better access to mental health services, where 64% of people reported that there is some mental health support available to them. Compare this to refugees in Lebanon, where only 15% believe there is some mental health support available and IDPs in Idlib where only 1% say this
- Female respondents suffer from more symptoms than males. 52% of females who have experienced at least one life threatening event have 10 more PTSD symptoms, and 88% have seven or more, compared to 37% of males who have 10 or more and 84% who have seven or more
- Under 18s are more likely to develop symptoms of PTSD being born into and living in an active warzone, than refugee children (100% of under 18s in Idlib have PTSD symptoms, compared to 60% in Lebanon and 69% in Turkey)

Syria Relief are calling for:

- Donor governments and international bodies to increase funding for mental health projects conducted by NGOs.
- When responding to the humanitarian impacts on conflicts, as well as treating the visible damage to buildings and bodies, the aid community must also take into account the mental health impact. NGOs need to be supported in providing refugees with mental health first aid and holistic protection interventions, to ensure all basic needs are met, including mental health support.
- Act immediately in order to stop the mental health crisis worsening.
- All warring parties in the conflict and their external allies need to push for a cessation of violence and the protection of civilian life immediately, as the war is the root cause of this PTSD crisis.
- The targeting of civilian life, which has traumatized the majority of Syrians, is a war crime and against international humanitarian law and international human rights law, there needs to be a real and considerable effort to find, try and bring to justice the perpetrators of the countless crimes against humanity committed in the Syrian conflict.
- Integrate refugees into host communities in order to combat the poverty which exacerbates their mental health crisis.

The report, published in March 2021, also commemorates the 10th anniversary of the start of the Syrian conflict.

on the WEB

The Destruction You Can't See: A report into the prevalence of PTSD symptoms amongst IDPs and refugees from the Syrian conflict.
bit.ly/3e214B7

A Decade of Loss: Syria's Youth After Ten Years of Crisis

Read the new report from the International Committee of the Red Cross, titled: "A Decade of Loss: Syria's Youth After Ten Years of Crisis" – published online on our new and enhanced website – *www.MiddleEastHealth.com* – The report looks in detail at how 10 years of war has robbed an entire generation of Syrians of their youth. Visit: *bit.ly/3eB0j22*

What is PTSD?

According to the American Psychiatric Association, Post Traumatic Stress Disorder (PTSD) is a psychiatric disorder that may occur in people who have experienced or witnessed a traumatic event such as a natural disaster, a serious accident, a terrorist act, war/combat, or rape or who have been threatened with death, sexual violence or serious injury.

PTSD has been known by many names in the past, such as "shell shock" during the years of World War I and "combat fatigue" after World War II, but PTSD does not just happen to combat veterans. PTSD can occur in all people, of any ethnicity, nationality or culture, and at any age.

People with PTSD have intense, disturbing thoughts and feelings related to their experience that last long after the traumatic event has ended. They may relive the event through flashbacks or nightmares; they may feel sadness, fear or anger; and they may feel detached or estranged from other people. People with PTSD may avoid situations or people that remind them of the traumatic event, and they may have strong negative reactions to something as ordinary as a loud noise or an accidental touch.

Many people with PTSD need professional treatment to recover from psychological distress that can be intense and disabling.

AI predicts efficacy of breast cancer treatment directly from tumour architecture

Researchers from the University of Helsinki have demonstrated the possibilities of artificial intelligence-based algorithms in predicting the efficacy of a targeted cancer therapy based on the tumour tissue architecture only, without specific molecular tests. The results suggest that AI can reveal previously hidden patterns in tumour samples and allow discovery of novel tumour features predictive of outcome and efficacy of treatment.

Artificial intelligence (AI) in the form of machine learning is increasingly used in cancer research and holds great potential in support of medical diagnostics. Algorithms have already been trained to tackle many complicated tasks such as detection of cancerous tissue and tumour grading. Also, prediction of disease outcome directly from a tumour sample without expert interpretation has shown promising results.

In a study published in *Scientific Reports* on February 17, a team led by Professor Johan Lundin aimed to push the capabilities of these approaches even further.

The researchers focused on developing a tool that could detect tumour morphological features typical for *ERBB2*-positive breast cancer. *ERBB2* (also frequently called HER2) is a well-known oncoprotein that promotes the growth of cancer cells. Approximately every fifth breast cancer patient has extra copies of the *ERBB2* gene and their tumours overexpress the *ERBB2* protein. These patients can benefit from therapy with monoclonal antibodies against the *ERBB2* (HER2) receptor.

The results of the study showed that the AI-algorithm was able to learn patterns predictive of the ERBB2 status of a tumour directly from the tumour morphology in a nationwide series of patients with breast cancer (the FinProg Study), without the use of specific molecular assays.

"Our results show that morphological features of tumours contain vast information about the biology of the disease that can be extracted with machine learning methods. This valuable data can aid in clinical decision-making," said the first author of the study, Dmitrii Bychkov from the Institute for Molecular Medicine Finland (FIMM), University of Helsinki.

To test the applicability of the method further, the researchers next applied the AI-algorithm to tissue samples from breast cancer patients that had participated in a large clinical trial (the FinHer trial) on anti-*ERBB2* treatment and whose *ERBB2* status and outcomes were known.

Interestingly, the algorithm was able to discriminate the patients treated with anti-*ERBB2* therapy (trastuzumab), a targeted treatment for *ERBB2*-positive cancers,

Professor Johan Lundin, Research Director at the Institute for Molecular Medicine Finland (FIMM), Nordic EMBL Partnership for Molecular Medicine, University of Helsinki.

into two prognostically different groups. Those patients in whose tumours the AI-algorithm predicted to be *ERBB2*-positive based on tumour morphology were shown to have a more favourable disease out-

> These AI-based methods open up new opportunities to reveal patterns hidden in the tissue architecture that drive tumour progression.

come than those predicted by the AI to be *ERBB2* negative.

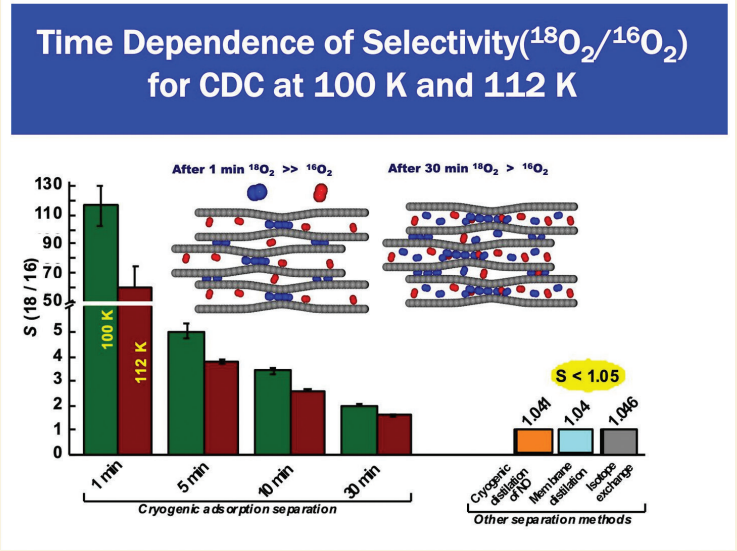
"These AI-based methods open up new opportunities to reveal patterns hidden in the tissue architecture that drive tumour progression and can in a longer perspective contribute to more precise diagnostics and better personalized treatment decisions in breast cancer," said Associate Professor Nina Linder, MD, who co-supervised the study.

The observations of the study also suggest that some of the tumours that were *ERBB2*-negative according to molecular tests have morphological features typical for ERBB2-positive tumours. According to the researchers, these patients might potentially benefit from treatments tailored for *ERBB2*-positive patients.

"The AI-based methods might not only complement the current molecular diagnostic methods but might go even beyond and lead to improved selection of some targeted cancer treatments for patients. We may need to design clinical trials to test this hypothesis. Importantly, the assay can be done from standard tumour section," said Professor Heikki Joensuu from the HUS Comprehensive Cancer Center and University of Helsinki who co-authored the study.

"This is one of the very first studies showing that AI applied to tumour samples can not only predict outcome of the disease, but also the efficacy of a molecularly targeted cancer treatment," said Prof Lundin.

Reference:
https://doi.org/10.1038/s41598-021-83102-6



Comparison of S at different times at 100 K and 112 K for the CDC in this work with other separation methods from the literature. The inset shows illustrative models for the pore filling of CDC by O2-16 and O2-18 molecules after 1 min and 30 min.

An efficient method for separating O-18 from O-16, essential for use in cancer treatment

Positron Emission Tomography (PET) plays a major role in the early detection of various types of cancer. A research group led by Specially Appointed Professor Katsumi Kaneko of the Research Initiative for Supra-Materials (RISM), Shinshu University have discovered a method to separate oxygen-18 from oxygen-16, an essential isotope for PET diagnosis, at high speed and high efficiency. The results of this research were recently published online in the journal *Nature Communications*.

The novel method for the rapid and efficient separation of O-18 from O2-16, which is abundant in the atmosphere, was carried out with nanoporous carbon, which is made of pores smaller than 1 nanometre. When a mixture of O2-16 and O2-18 is introduced into the nanoporous carbon, the O2-18 is preferentially adsorbed and is efficiently separated from O2-16. The experimental separation of O2-18 from O2-16 was also conducted using the low-temperature waste heat from a natural gas storage facility.

O-18 plays a major role in the early detection of cancer. Taking advantage of the property of cancer cells which take up much more glucose than normal cells, doctors inject a drug called 18F-FDG (fluorodeoxyglucose), which is an index of glucose metabolism and uses a PET machine to clarify which part of the body has cancer. 18F-FDG is a drug in which fluorine-18 (18F), which emits positive electricity, is attached to glucose. 18F-FDG is produced by a nuclear reaction in which O-18 is introduced before the protons are injected. Therefore, O-18 is an important substance indispensable for PET diagnosis but was difficult to procure because only 0.2% of naturally occurring oxygen is O-18. In order to separate O-18 from the majority of O-16 found in the atmosphere, it was necessary to distil O-18 from O-16, even though they have very similar boiling points. This distillation required precise technology and took more than 6 months to complete.

The novel method using nanoporous carbon to distil O-18 can be used not only for PET diagnosis but for research on dementia, and this novel method can be applied to the separation of carbon and nitrogen isotopes, and other molecules useful for isotopic analysis methods and therapeutic cancer drugs. The group expects more demand for this method and substance in the future.

Reference:
https://doi.org/10.1038/s41467-020-20744-6

Ionic liquid formulation uniformly delivers chemotherapy to tumours while destroying cancerous tissue

A Mayo Clinic team, led by Rahmi Oklu, M.D., Ph.D., a vascular and interventional radiologist at Mayo Clinic, in collaboration with Samir Mitragotri, Ph.D., of Harvard University, report the development of a new ionic liquid formulation that killed cancer cells and allowed uniform distribution of a chemotherapy drug into liver tumours and other solid tumours in the lab. This discovery could solve a problem that has long plagued drug delivery to tumours and provide new hope to patients with liver cancer awaiting a liver transplant. The preclinical study results are published in *Science Translational Medicine*.

Dr Oklu, study author and director of Mayo Clinic's Minimally Invasive Therapeutics Laboratory, said uniform drug delivery to tumours is often riddled with challenges. It's an issue he and the research team are aiming to solve, particularly for patients with liver cancer who are awaiting a transplant.

Dr Oklu said higher drug doses are often used to encourage drug delivery into the tumour, and these higher doses could lead to significant toxicity. "If the drug cannot penetrate the tumour and remain there, then it cannot do its job," he explained.

Current treatment involves ablation, which involves heating or cooling the tumour or infusing radioactive particles into the arteries of the tumour to destroy the cancer cells and keep patients within the criteria for a transplant.

"You could do a microwave ablation and basically burn the tumour, but that is often not an option if the tumour is close to the heart or other important structures. And sometimes it is hard to find the blood supply of the tumour to infuse the radioactive particles," Dr Oklu added.

Dr Oklu and his colleagues developed an ionic liquid – essentially salt in a liquid state – as an alternative way to deliver drugs into tumours through an ultrasound-guided needle injection. Once injected, the authors say the ionic liquid deposited the chemotherapy drugs uniformly, killing the cancer cells as the liquid engulfed the tumours.

Preclinical studies

The researchers reported this approach was successful in preclinical studies using freshly resected human tumours in the lab and liver tumours in animal models. In addition, the authors report that the chemotherapy remained in the targeted zone for the length of the 28-day trial.

Whereas drugs often wash away quickly from direct injection into tumours or from standard IV delivery of chemotherapy through the veins of the arm, the ionic liquid, which the authors call a "locally active agent for tumour treatment and eradication," or LATTE, also encouraged immune cell infiltration in the microenvironment of the tumour. This may play a role in achieving immunotherapy in solid tumours. The researchers say this could solve current challenges, especially in hepatocellular carcinoma – the most common form of liver cancer – where liver transplant can be curative.

"Ionic liquids are an exceptionally versatile group of materials. In our lab, we have already demonstrated that they have the ability to overcome a variety of biological barriers within the body for delivering drugs. In this study, we demonstrate a novel application of ionic liquids to deliver chemotherapeutic drugs in the liver tumour," said Dr Mitragotri.

Rahmi Oklu, M.D., Ph.D., vascular and interventional radiologist at Mayo Clinic

The authors suggest that LATTE may work via diverse methods, and future studies are planned to expand on these preclinical findings. Future efforts might examine additional chemotherapy drugs, effects of immunotherapy agents and effects on overall survival, and involve a detailed analysis of local and bodywide immune implications of this experimental intervention.

In addition to Dr Oklu, Mayo Clinic authors include lead author Hassan Albadawi, M.D.; Zefu Zhang, M.D.; Izzet Altun, M.D., Jingjie Hu, Ph.D., and Leila Jamal. In addition to Dr Mitragotri, authors from Harvard University are Kelly Ibsen, Ph.D., and Eden Tanner, Ph.D.

Reference:
https://doi.org/10.1126/scitranslmed.abe3889

DigiHealth Middle East

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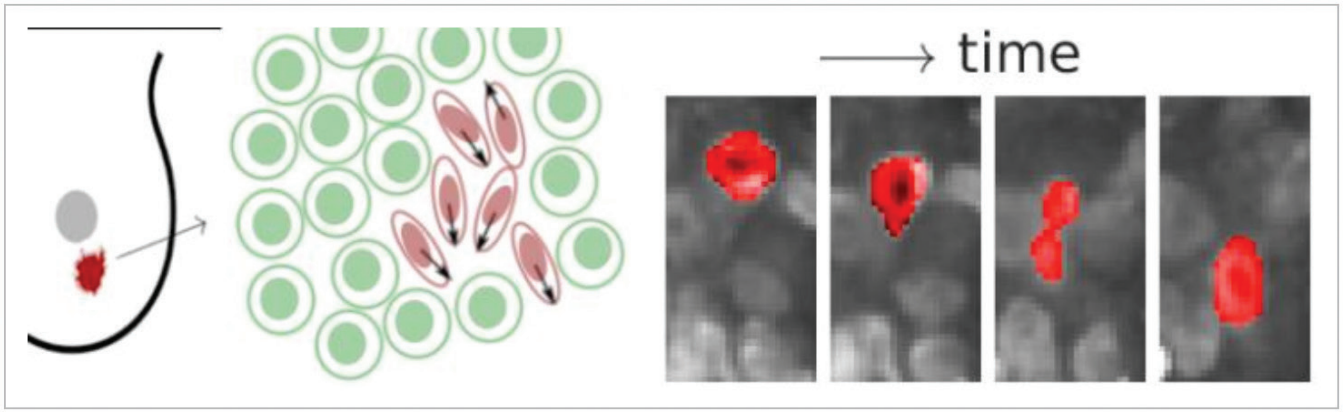

Steffen Grosser, Leipzig University

Researchers at Leipzig University found fluid and solid regions in breast and cervical tumours. The fluid regions can be recognised by elongated cells that squeeze through the dense tumour tissue.

Physics of tumours: Cancer cells become fluidised and squeeze through tissue

Working with colleagues from Germany and the US, researchers at Leipzig University have achieved a breakthrough in research into how cancer cells spread. In experiments, the team of biophysicists led by Professor Josef Alfons Käs, Steffen Grosser and Jürgen Lippoldt demonstrated for the first time how cells deform in order to move in dense tumour tissues and squeeze past neighbouring cells. The researchers found that motile cells work together to fluidise tumour tissue.

Prof Käs led the research project in cooperation with Professor Lisa Manning from Syracuse University (US) and Professor Bahriye Aktas from Leipzig University Hospital. They have published their findings in *Physical Review X*, a leading journal that primarily publishes groundbreaking research results.

"These first observations of a phase transition in human tumours change our basic concepts of tumour progression and could improve cancer diagnosis and therapy," said Käs, who has been studying the physical properties of cancer cells for years. He said the research showed that human tumours contain solid and fluid cell clusters, which would be a breakthrough in scientists' understanding of tumour mechanics. He added that the results form the basis for the first procedure with which metastatic cancer cells can already be detected in the tumour.

In tumour samples from patients at Leipzig University Hospital, the researchers found regions with motile cells as well as stable, solid-like regions with no cell movement. From a physical point of view, cells should not be able to move in the dense tumour mass – tumours are so densely crowded with cells that motion would be inhibited in any typical material.

The researchers therefore developed a new approach to live tumour microscopy by fluorescently staining human tumour samples immediately after surgery, allowing them to observe cell movement live. This led them to discover that, contrary to all previous findings, this cell motility does indeed take place and is associated with strong nuclear deformation. They observed how cells and their nuclei literally squeeze through the tissue by becoming severely deformed.

"Cells in biological tissues behave much like people in a bar. At low densities, they can move freely. However, movement becomes difficult when things get very crowded. But even in a crowded bar, you can still squeeze past if you turn sideways. This is exactly the effect we see in tumour tissues," said Prof Käs. The researchers believe this phase transition explains how cells can move and multiply in a tumour, eventually leading to metastasis. The fluid tissues showed elongated, deformed cells and nuclei. Static images of elongated cell and nuclear shapes could thus serve as a fingerprint for the metastatic aggressiveness of a tumour.

"These are spectacular results from the field of cancer physics. We now need to investigate whether the fluid regions can predict tumour aggressiveness. Here we have found a cancer marker that indicates active, motile regions and that is based on a simple physical mechanism," said Steffen Grosser.

Prof Käs is currently embarking on a clinical trial to investigate the potential of cell and nuclear shape as a new tumour marker that could be used to examine and treat patients in a much more targeted way than before.

Reference:

https://journals.aps.org/prx/abstract/10.1103/PhysRevX.11.011033

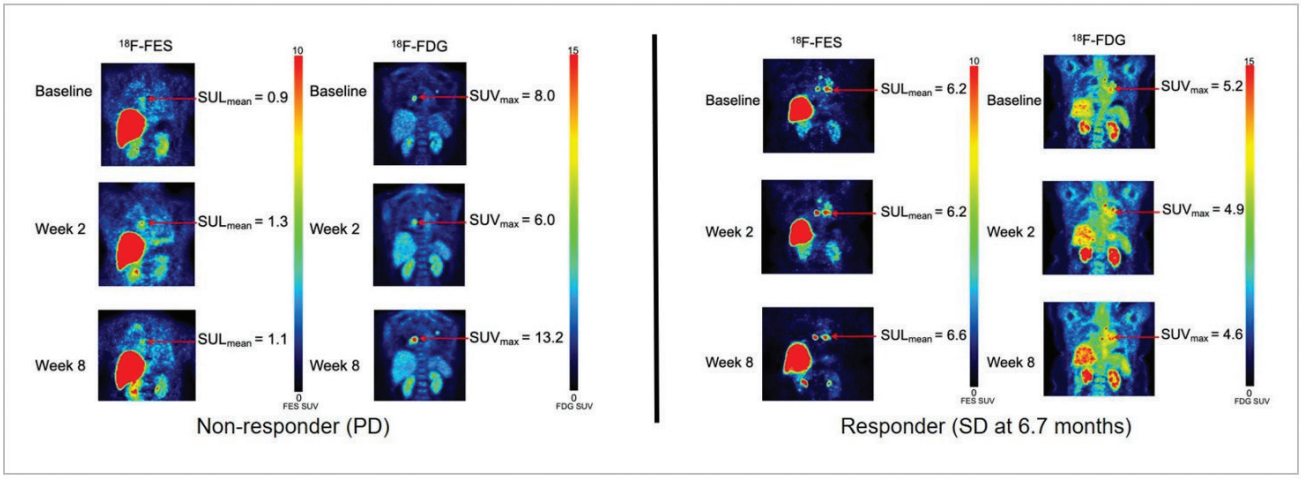

Image created by Lanell M Peterson, Research Scientist, University of Washington Medical Oncology, Seattle WA.

F-18 FES PET images of patients with ER+/PR+/HER2- invasive ductal carcinoma. Left panel: Progressive disease seen at the 8-week time-point in a patient on sequential therapy. Right panel: Stable disease through all 3 time-points, remaining on study therapy for 6.7 months until disease progression on combined vorinostat aromatase inhibitor therapy.

Molecular imaging determines effectiveness of novel metastatic breast cancer treatment

Molecular imaging can successfully predict response to a novel treatment for ER-positive, HER2-negative metastatic breast cancer patients who are resistant to hormonal therapy. According to research published in the February issue of the *Journal of Nuclear Medicine*, positron emission tomography (PET) imaging using an imaging agent called 18F-fluoroestradiol can help to determine which patients could benefit from treatments that could spare them from unnecessary chemotherapy.

Nearly two-thirds of invasive breast cancers are ER-positive, and endocrine therapy is the mainstay of treatment for these tumours because of its favourable toxicity profile and efficacy. Should cancer progress in these patients, however, salvage endocrine therapy with molecularly targeted agents or chemotherapy can help.

"In some ER-positive breast cancer patients, cancer progression can be a result of a gradual resistance to endocrine therapy," noted Hannah M Linden, MD, FACP, Athena Distinguished Professor and breast medical oncologist at the University of Washington Fred Hutchison Cancer Research Center and Seattle Cancer Care Alliance in Seattle, Washington. "Histone daecetylase inhibitors (HDACIs) have been proposed as a mechanism to reverse endocrine resistance, and clinical studies have shown promising results when combining endocrine therapy with HDACIs to restore endocrine sensitivity."

To further explore the efficacy of this combination therapy, researchers designed a study in which 18F-FDG PET imaging with 18F-fluoroestradiol was conducted on patients receiving vorinostat, a potent HDACI, along with an aromatase inhibitor, a type of endocrine therapy. Scans were performed at baseline, week two and week eight of the study. Subjects included ER-positive/HER2-negative breast cancer patients who had previously responded well to endocrine therapy while on an aromatase inhibitor. Eight of the study participants were treated with vorinostat followed by an aromatase inhibitor, while 15 were treated with both at the same time.

After eight weeks, eight patients had stable disease, and six of the eight patients were stable for more than six months. Higher baseline 18F-fluoroestradiol uptake was associated with longer progression-free survival. 18F-fluoroestradiol uptake did not systematically increase with vorinostat exposure, indicating no change in regional ER estradiol binding, and 18F-FDG uptake did not show a significant decrease, which is expected with tumour regression.

"We test ER expression in a metastatic biopsy once at the beginning of the patient's journey," explained Linden, "and we make decisions all along--when to give chemotherapy, when to use endocrine therapy, whether or not to use targeted agents – based on that one measurement. Since we know that ER expression can fluctuate, imaging with 18F-fluoroestradiol at various time points could help clinicians predict response to endocrine therapy and select optimal treatment in the future."

18F-fluoroestradiol was approved by the U.S. Food and Drug Administration in May 2020. MEH

Interview

Dubai's new Fakeeh University Hospital to combine clinical care and medical education on single campus

The 350-bed Fakeeh University Hospital – part of Fakeeh Care in Saudi Arabia – has recently opened in Dubai's Silicon Oasis. *Middle East Health* speaks to Dr David Saxton, the Chief Medical and Clinical Officer, about the hospital.

***Middle East Health*: Can you tell us a bit about the hospital set-up?**

Dr David Saxton: Fakeeh University Hospital (FUH) is a four-building institute equipped with advanced operating theatres, radiology, and diagnostics. It has the largest private sector emergency department in Dubai. We have a total capacity of 13 operating rooms – 12 standard operating rooms and an additional one situated within the Women's Health Unit for childbirth and emergencies. In addition to that, our hospital also features one of the largest laboratories in Dubai.

FUH has 350 inpatient beds, three Intensive Care Units, including a paediatric ICU and a neonatal ICU. The hospital also has a total capacity for 55 outpatient clinics.

***MEH*: What are the key specialties that the hospital will focus on?**

DS: As a University Hospital, we must provide all the core services that one would typically find in a university hospital, so that all our patients' healthcare needs can be met. However, looking at the city's urban plan and the development of new communities in the Dubai Silicon Oasis area and beyond, we are anticipating an increased need for Women and Child Health. As a result, we have established a Women's Health Unit.

Orthopaedics is also one of our focus areas, and we are looking to establish a Sports Medicine Academy. Cardiology and Critical Care are also key specialities. Thanks to our large bed capacity, we have an opportunity to provide a very robust critical care service. Even though we are a start-up facility, we have a fully operating Critical Care Ward, which is currently serving Covid-19 patients.

***MEH*: As a university hospital, which university or universities is FUH affiliated to?**

DS: Fakeeh University Hospital is bringing a rather unique experience to the UAE, particularly to the private sector, where both an academic and clinical unit are combined on one campus. Our teaching hospital in Dubai will be affiliated with the Fakeeh College of Medical Sciences, which we established in 2003 in the Kingdom of Saudi Arabia and which has proven to be a very successful model. The vast footprint of Fakeeh Care hospitals and clinics in the Kingdom and our 43-year legacy has taught us how innovation at the heart of care can drive the quality to unparalleled levels. For example, the foundation hospital performed the first IVF in the Kingdom of Saudi Arabia, bringing several other firsts as well, including the first renal transplant in 1985, and the first heart transplant in 1990. And so, with this strong foundation for innovation we have come to the UAE with this academic model and are already working with the local authorities to have Fakeeh University Hospital identified as a satellite campus for the UAE and wider region.

Dr David Saxton, the Chief Medical and Clinical Officer, Fakeeh University Hospital

***MEH*: So it will serve as a teaching hospital for medical students?**

DS: Yes, Fakeeh University Hospital will serve as a teaching hospital, however we will be our own academic entity and will not be implementing a rotation concept where students are rotating from campus to campus.

While our university campus is awaiting

development, we have had some preliminary exploration with other international academic organizations and our College in Jeddah with regards to course curriculum design and development. As we move forward with our university campus, we will be looking at emulating our model in Jeddah to provide undergraduate courses for nursing, medicine, and allied health sciences studies, such as physiotherapy and emergency care training, followed by postgraduate studies.

Fakeeh University Hospital will have a university capacity of up to 3000 students.

***MEH*: FUH will also serve as a research facility. Can you give us an idea of what research is planned and who will be conducting it?**

DS: Our Foundation hospital in Saudi Arabia has been approaching medical research from a different perspective, looking at clinical outcomes, modifying treatments and studying their impact. A lot of the research has also been conducted in the laboratory. For example, the Middle East Respiratory Syndrome (MERS) was first discovered in 2012 in a lab at Dr Soliman Fakeeh Hospital.

Research will be an integral part of Fakeeh University Hospital. Though there will remain a focus on developing new strategies for the COVID and post-COVID eras, we shall continue to pursue the principles of a customised precision approach to clinical management through new technologies and development of multimodal treatment programmes. In essence the research will aim to address the respective needs and challenges of the time and shall be initiated by FUH physicians as well as in partnership with our hospital and college in Jeddah and other academic institutes locally, regionally and internationally.

***MEH*: Why did Fakeeh Care decide to establish a hospital in Dubai?**

DS: Through Fakeeh Care's operations in Saudi over the past four decades, we have achieved a successful model for care delivery at high international standards, which we decided to export to the UAE. There is no doubt that Dubai has become

an international platform with a well-established healthcare sector, whether it's from an infrastructure or talent perspective. However, our market research indicated the need for an institute, bringing together locally and regionally based talent and medical research, underpinned by academia, all under one umbrella.

The UAE healthcare market is rich in diverse providers and specialities, but can also be quite fragmented, whereby many facilities follow a single-focused hospital model, each specializing in few therapy areas. This means however that patients may experience a disruption in their treatment and recovery journey, especially if they need care in other clinical areas that require external expertise. Therefore, we wanted to bring an all-inclusive multidisciplinary care model, founded in academics with primary, secondary and tertiary care across 55 specialities.

***MEH:* Does Fakeeh Care have other healthcare facilities outside the Kingdom of Saudi Arabia? Do they plan to establish others?**

DS: Fakeeh University Hospital in Dubai is the first expansion project for the group outside of the Kingdom. Over recent years, Fakeeh Care has received several operational investment requests from the GCC and a number of African countries. However, the focus at present is on our operations in the UAE and KSA.

***MEH:* The pharmacy has a state-of the-art digital dispensary. Can you tell us about some of the other new digital MedTech at the hospital?**

DS: The hospital has one of the largest robotic pharmacies in the UAE that minimizes human errors in dispensing medications, which is a significant cause of morbidity and mortality throughout the world.

Having an integrated system allows us to track every single tablet, from the point at which it is delivered to the hospital, when it is stored in the pharmacy to the point of care, when it is provided to the patient. This is not just thanks to the robotic pharmacy; it is the result of integration of our overall healthcare information system. This also means the collection of data at every point of care is essential, as it automatically populates the hospital information system. By accessing data in a timely fashion, we are able significantly reduce the chances of medical error.

Fakeeh University Hospital also utilizes its advanced hospital information system to provide real-time connectivity between patients, their families and caregivers within the hospital and remotely. Our patients shall have direct access through the website or our mobile App to book their in-hospital, remote or home-care appointments. Within FUH clinical data is automatically integrated into the electronic medical record at the point of care. Telemetry is available throughout the organisation, as indeed will be remote monitoring from the home. Inpatients shall have access to our advanced infotainment system which not only provides access to multimedia and entertainment but direct access to their clinical data and daily care plans, health updates and healthcare education.

Our facility also utilizes some of the most advanced imaging systems available in radiology, as well as technologies for image-guided interventions, cardiac catheterization, and peripheral vascular interventions.

***MEH:* Staffing a hospital is a challenging task, but is key to providing trusted and quality care. Can you tell us how the hospital approached this challenge and from where you have recruited your doctors and nurses?**

DS: When recruiting for our hospital, we looked at physician and nurse leaders within the existing UAE workforce for several reasons. The UAE is home to a lot of clinical talent, which the Emirates have attracted over the years. In addition to that, we were looking for professionals who understood the UAE's dynamic and multi-cultural environment and who can work together as part of a team.

We handpicked talent based on their experience, integrity, teamwork, social responsibility, patient-focused concept, values of compassion and most importantly accountability. We also looked for that spark of innovation.

As a result of that recruitment hunt, we were able to find clinicians with a proven track record and reputation, who had adjusted to the environment and most importantly who fitted perfectly within the organization. We have been pleasantly surprised by the relative ease at which we have been able to attract interest from talented healthcare practitioners. We found a very receptive group of clinicians waiting for an organization to give them the opportunity to do things differently.

The key to recruiting successfully from a relatively limited workforce is having a physician-led approach, great core leaders, and the right innovation and philosophy in place, which then permeates and becomes the norm for the organization.

***MEH:* As a last word, is there anything you'd like to add?**

DS: Fakeeh University Hospital is set to be more than just a hospital; we are bringing a 43-year legacy that champions innovation in all aspects of care delivery. In 2009, we established home healthcare services through our ambulatory homecare visits, even before opening the doors of our hospital, and we are looking to export our Fakeeh Care portfolio of wellness and fitness, medical education, digital health and integrated care.

Furthermore, we have a phased approach that allows us with time to evaluate what the community's needs are and redefine our capacity planning. This means that we can exploit our 350-bed capacity with some of the space and resources directed towards the development of clinical institutes for sports medicine, neurosciences or a cardio-metabolic centre. Our legacy has taught us to shift from the concept of departmentalized services to disease-based services, so that our patients can receive holistic care.

We are alos in the process of ensuring Fakeeh University Hospital is recognized as a centre of excellence by numerous international accreditation bodies, such as Planetree, Magnet, the American Society for Health Systems Pharmacists, the College of American Pathologists, ISO and the American Heart Association, amongst others.

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General anaesthesia has been in use for nearly 175 years, but its mechanism for causing loss of consciousness has been unknown until now. So momentous was the first use of ether that it was memorialized in this painting, "First Operation Under Ether," by Robert C. Hinckley. /

Anaesthesia's effect on consciousness solved

Surgery would be inconceivable without general anaesthesia, so it may come as a surprise that despite its 175-year history of medical use, doctors and scientists have been unable to explain how anaesthetics temporarily render patients unconscious.

A new study from Scripps Research in the *Proceedings of the National Academies of Sciences* (PNAS) solves this longstanding medical mystery. Using modern nanoscale microscopic techniques, plus clever experiments in living cells and fruit flies, the scientists show how clusters of lipids in the cell membrane serve as a missing go-between in a two-part mechanism. Temporary exposure to anaesthesia causes the lipid clusters to move from an ordered state, to a disordered one, and then back again, leading to a multitude of subsequent effects that ultimately cause changes in consciousness.

The discovery by chemist Richard Lerner, MD, and molecular biologist Scott Hansen, PhD, settles a century-old scientific debate, one that still simmers today: Do anaesthetics act directly on cell-membrane gates called ion channels, or do they somehow act on the membrane to signal cell changes in a new and unexpected way? It has taken nearly five years of experiments, calls, debates and challenges to arrive at the conclusion that it's a two-step process that begins in the membrane, the duo say. The anaesthetics perturb ordered lipid clusters within the cell membrane known as "lipid rafts" to initiate the signal.

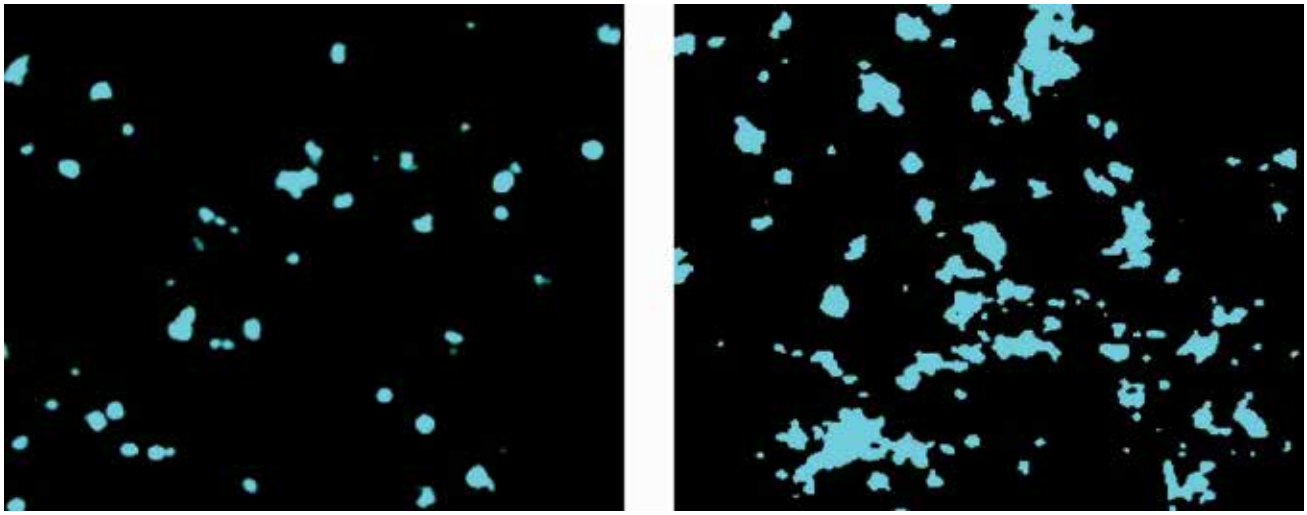
"We think there is little doubt that this novel pathway is being used for other brain functions beyond consciousness, enabling us to now chip away at additional mysteries of the brain," Lerner says.

Lerner, a member of the National Academy of Sciences, is a former president of Scripps Research, and the founder of Scripps Research's Jupiter, Florida campus. Hansen is an associate professor at that same campus.

The Ether Dome

Ether's ability to induce loss of consciousness was first demonstrated on a tumour patient at Massachusetts General Hospital in Boston in 1846, within a surgical theatre that later became known as "the Ether Dome". So consequential was the procedure that it was captured in a famous painting, "First Operation Under Ether," by Robert C. Hinckley. By 1899, German pharmacologist Hans Horst Meyer, and then in 1901 British biologist Charles Ernest Overton, sagely concluded that lipid solubility dictated the potency of such anaesthetics.

Hansen recalls turning to a Google search while drafting a grant submission to investigate further that historic question, thinking he couldn't be the only one convinced of membrane lipid rafts' role. To Hansen's delight, he found a figure from Lerner's 1997



Hansen lab, Scripps Research.

An ordered cholesterol cluster in a cell membrane briefly becomes disordered on exposure to chloroform. As the lipid cluster spills its contents, dSTORM microscopy reveals that it releases PLD2 molecules, which cause further disruption as they disperse, ultimately activating potassium channels.

PNAS paper, "A hypothesis about the endogenous analogue of general anaesthesia," that proposed just such a mechanism. Hansen had long looked up to Lerner – literally. As a predoctoral student in San Diego, Hansen says he worked in a basement lab with a window that looked directly out at Lerner's parking space at Scripps Research.

"I contacted him, and I said, 'You are never going to believe this. Your 1997 figure was intuitively describing what I am seeing in our data right now,'" Hansen recalls. "It was brilliant."

For Lerner, it was an exciting moment as well.

"This is the granddaddy of medical mysteries," Lerner says. "When I was in medical school at Stanford, this was the one problem I wanted to solve. Anaesthesia was of such practical importance I couldn't believe we didn't know how all of these anaesthetics could cause people to lose consciousness."

Many other scientists, through a century of experimentation, had sought the same answers, but they lacked several key elements, Hansen says: First, microscopes able to visualize biological complexes smaller than the diffraction limits of light, and second, recent insights about the nature of cell membranes, and the complex organization and function of the rich variety of lipid complexes that comprise them.

"They had been looking in a whole sea of lipids, and the signal got washed out, they just didn't see it, in large part for a lack of technology," Hansen says.

From order to disorder

Using Nobel Prize-winning microscopic technology, specifically a microscope called dSTORM, short for "direct stochastical optical reconstruction microscopy", a post-doctoral researcher in the Hansen lab bathed cells in chloroform and watched something like the opening break shot of a game of billiards. Exposing the cells to chloroform strongly increased the diameter and area of cell membrane lipid clusters called GM1, Hansen explains.

What he was looking at was a shift in the GM1 cluster's organization, a shift from a tightly packed ball to a disrupted mess, Hansen says. As it grew disordered, GM1 spilled its contents, among them, an enzyme called phospholipase D2 (PLD2).

Tagging PLD2 with a fluorescent chemical, Hansen was able to watch via the dSTORM microscope as PLD2 moved like a billiard ball away from its GM1 home and over to a different, less-preferred lipid cluster called PIP2. This activated key molecules within PIP2 clusters, among them, TREK1 potassium ion channels and their lipid activator, phosphatidic acid (PA). The activation of TREK1 basically freezes neurons' ability to fire, and thus leads to loss of consciousness, Hansen says.

"The TREK1 potassium channels release potassium, and that hyper-polarizes the nerve – it makes it more difficult to fire – and just shuts it down," Hansen says.

Lerner insisted they validate the findings in a living animal model. The common fruit fly, *drosophila melanogaster*, provided that data. Deleting PLD expression in the flies rendered them resistant to the effects of sedation. In fact, they required double the exposure to the anaesthetic to demonstrate the same response.

"All flies eventually lost consciousness, suggesting PLD helps set a threshold, but is not the only pathway controlling anaesthetic sensitivity," they write.

Hansen and Lerner say the discoveries raise a host of tantalizing new possibilities that may explain other mysteries of the brain, including the molecular events that lead us to fall asleep.

Lerner's original 1997 hypothesis of the role of "lipid matrices" in signalling arose from his inquiries into the biochemistry of sleep, and his discovery of a soporific lipid he called oleamide. Hansen and Lerner's collaboration in this arena continues.

"We think this is fundamental and foundational, but there is a lot more work that needs to be done, and it needs to be done by a lot of people," Hansen says. Lerner agrees.

"People will begin to study this for everything you can imagine: Sleep, consciousness, all those related disorders," he says. "Ether was a gift that helps us understand the problem of consciousness. It has shined a light on a heretofore unrecognized pathway that the brain has clearly evolved to control higher-order functions."

Reference:

Studies on the mechanism of general anaesthesia. PNAS
May 28, 2020. doi: *https://doi.org/10.1073/pnas.2004259117*

Imaging the Twilight Zone – General anaesthesia and normal sleep affect brain in an amazingly similar way as consciousness fades

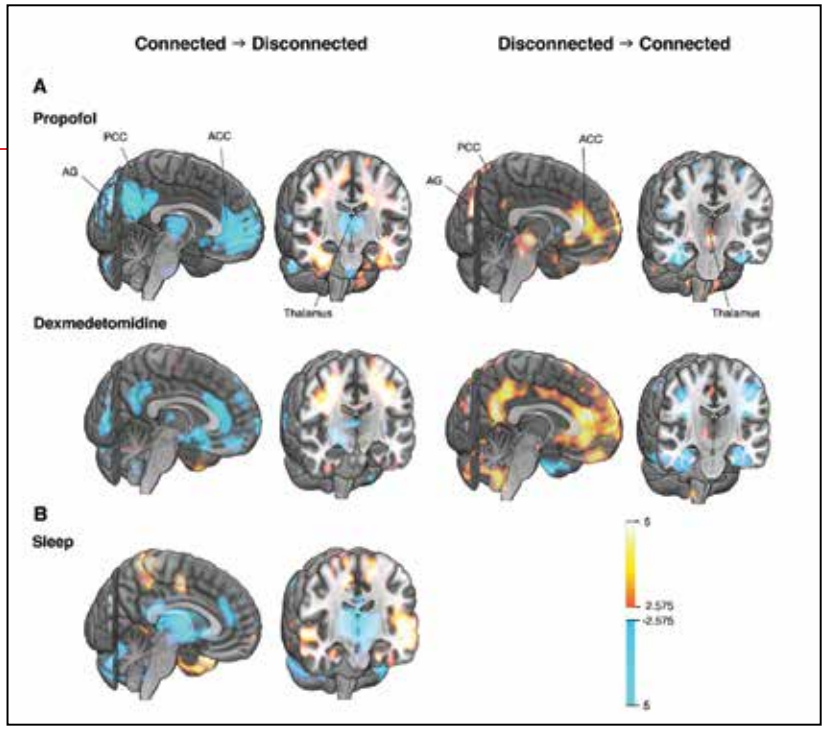


Image courtesy the University of Turku.

Differences in brain activity between connected and disconnected states of consciousness studied with positron emission tomography (PET) imaging. Activity of the thalamus, anterior (ACC) and posterior cingulate cortices (PCC), and bilateral angular gyri (AG) show the most consistent associations with the state of consciousness (A = general anaesthesia, B = sleep). The same brain structures, which are deactivated when the state of consciousness changes to disconnected in general anaesthesia or natural sleep (cool colours in the left columns), are reactivated when regaining a connected state upon emergence from anaesthesia (warm colours in the right columns).

What happens in the brain when our conscious awareness of the surrounding world and of ourselves fades during general anaesthesia and normal sleep? This fundamental question was studied with novel experimental designs and functional brain imaging by Finnish scientists [1]. They succeeded in separating the specific changes related to consciousness from the more widespread overall effects, commonly misinterpreted as the neural correlates of consciousness. The effects of anaesthesia and sleep on brain activity turned out to be surprisingly similar. These novel findings point to a common central core brain network that is fundamental for human consciousness.

Explaining the biological basis of human consciousness is one of the greatest challenges of science. While the loss and return of consciousness, as regulated by drugs or physiological sleep, have been employed as model systems in the study of human consciousness, previous research results have been confounded by many experimental simplifications.

"One major challenge has been to design a set-up, where brain data in different states differ only in respect to consciousness. Our study overcomes many previous confounders, and for the first time, reveals the neural mechanisms underlying connected consciousness," says Harry Scheinin, Docent of Pharmacology, Anaesthesiologist, and the Principal Investigator of the study from the University of Turku, Finland.

Innovative experimental set-up

Brain activity was measured with positron emission tomography (PET) imaging during different states of consciousness in two separate experiments in the same group of healthy subjects. Measurements were made during wakefulness, escalating and constant levels of two anaesthetic agents, and during sleep-deprived wakefulness and Non-Rapid Eye Movement (NREM) sleep.

In the first experiment, the subjects were randomly allocated to receive either propofol or dexmedetomidine (two anaesthetic agents with different molecular mechanisms of action) at stepwise increments until the subjects no longer responded. In the sleep study, they were allowed to fall asleep naturally. In both experiments, the subjects were roused to achieve rapid recovery to a responsive state, followed by immediate and detailed interviews of subjective experiences from the preceding unresponsive period. Unresponsive anaesthetic states and verified NREM sleep stages, where a subsequent report of mental content included no signs of awareness of the surrounding world, indicated a disconnected state in the study participants. Importantly, the drug dosing in the first experiment was not changed before or during the shift in the behavioural state of the subjects.

"This unique experimental design was the key idea of our study and enabled us to distinguish the changes that were specific to the state of consciousness from the overall effects of anaesthesia," explains Annalotta Scheinin, Anaesthesiologist, Doctoral Candidate and the first author of the paper.

Common central core brain network

When PET images of responsive and connected brains were compared with those of unresponsive and disconnected, the scientists found that activity of the thalamus, cingulate cortices and angular gyri were affected independently of the used anaesthetic agent, drug concentration and direction of change in the state of consciousness (see figure). Strikingly analogous findings were obtained when physiological sleep was compared with sleep-deprived wakefulness. Brain activity changes were much more extensive when the disconnected states were compared with a fully awake state. State-specific findings were thus distinct and separable from the overall effects of drug-induced anaesthesia and natural sleep, which included widespread suppression of brain activity across cortical areas.

These findings identify a central core brain network that is fundamental for human consciousness.

"General anaesthesia seems to resemble normal sleep more than has traditionally been thought. This interpretation is, however, well in line with our recent electrophysiological findings in another anaesthesia study [2]," says Harry Scheinin.

Subjective experiences common during general anaesthesia

Interestingly, unresponsiveness rarely denoted unconsciousness (i.e., total absence

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of subjective experiences), as most participants reported internally generated experiences, such as dreams, in the interviews. This is not an entirely new finding as dreams are commonly reported by patients after general anaesthesia.

"However, because of the minimal delay between the awakenings and the interviews, the current results add significantly to our understanding of the nature of the anaesthetic state. Against a common belief, full loss of consciousness is not needed for successful general anaesthesia, as it is sufficient to just disconnect the patient's experiences from what is going on in the operating room," explains Annalotta Scheinin.

The new study sheds light on the fundamental nature of human consciousness and brings new information on brain functions in intermediate states between wakefulness and complete unconsciousness. These findings may also challenge our current understanding of the essence of general anaesthesia.

The experiments were carried out at Turku PET Centre as a joint effort of the research groups of Harry Scheinin studying anaesthesia mechanisms, and Professor of Psychology Antti Revonsuo studying human consciousness and the brain from the point of view of philosophy and psychology, in collaboration with Professor Michael Alkire from the University of California, Irvine, USA. Turku PET Centre is a Finnish National Research Institute established by University of Turku, Åbo Akademi University and Turku University Hospital. The study was funded by the Academy of Finland and the Jane and Aatos Erkko Foundation.

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[1] Foundations of human consciousness: Imaging the twilight zone. The Journal of Neuroscience. 28 December 2020
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[2] Differentiating Drug-related and State-related Effects of Dexmedetomidine and Propofol on the Electroencephalogram. Anesthesiology. July 2018, Vol. 129, 22–36.
doi: *https://doi.org/10.1097/ALN.0000000000002192*

New device decreases accidental cerebrospinal fluid leaks during epidural anaesthesia

Asociacion RUVID

Epidural anaesthesia is a technique that requires great accuracy to avoid accidentally puncturing the dura matter, one of the three meninx that protect the central nervous system. The cerebrospinal fluid, which feeds the nervous system, is located under the dura mater. Leaks of this fluid can cause strong headaches that can be crippling and delay recovery following an intervention with this anaesthetic technique. They are especially severe in women who suffer this complication after receiving an epidural while giving birth.

Researcher Carlos García Victoria has patented a device that decreases the leak of cerebrospinal fluid if it accidentally punctures the dura mater. Its successful validation in an ovine model, a necessary prior step for its application on humans, has been performed at the Veterinary Clinical Hospital by lecturers from the Department of Medicine and Animal Surgery of the Faculty of Veterinary Medicine and the Clinical Veterinary Hospital of the CEU Cardenal Herrera University (CEU UCH).

José Ignacio Redondo, Mireia García Roselló, Álvaro Gutiérrez and Vicente Esteve.

Researchers from several centres and universities took part in the design and creation of this innovative design.

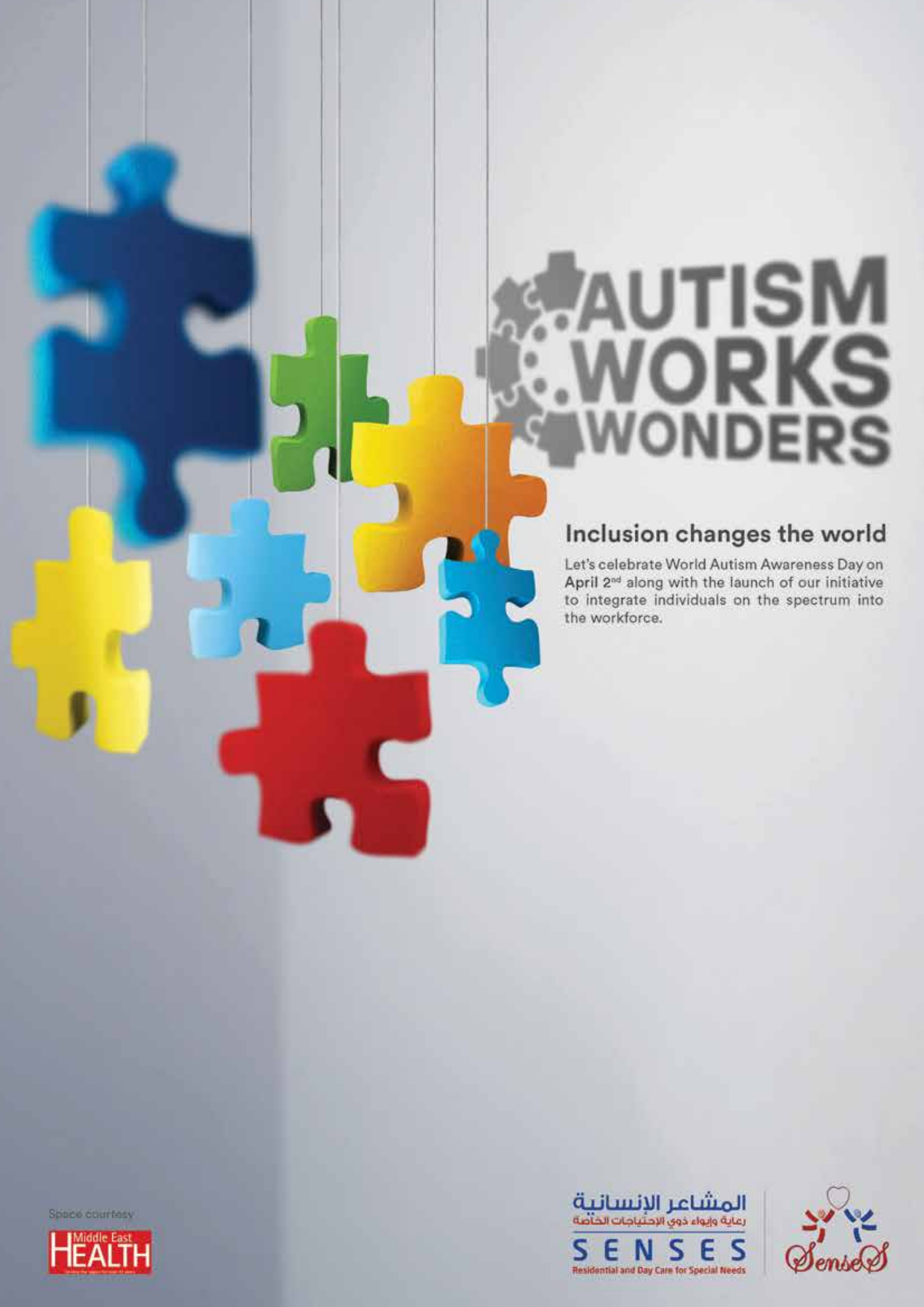
The device can be applied immediately after detecting an accidental puncture of the dura mater, sealing the cerebrospinal fluid leakage in a simple way. This would avoid the cause of the subsequent headaches, which can last several days or even weeks, extending hospital stays and recovery following the intervention.

Prior step for its use in humans

The results of its efficacy on an animal model have just been published in *Regional Anesthesia and Pain Medicine*. According to anaesthesiology lecturer from the Faculty of Veterinary Medicine of the CEU UCH, José Ignacio Redondo: "The design of this animal model has made it possible to successfully validate the efficiency of the device. This is the first necessary step for its use to be authorised on humans."

Reference:

Validation of a bioabsorbable device that seals perforations after Tuohy needle dural puncture in an ovine model. *Regional Anesthesia and Pain Medicine*.
doi: *10.1136/rapm-2020-102225*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Finding sustainable ways to address gender inequity in eye health

By **Rashin Choudhry**
Program Development Advisor,
The Fred Hollows Foundation

More than 20 million women are blind and a further 120 million live with vision impairment. We know that four out of five people who are blind do not need to be, yet women are 1.3 times more likely to be blind than men.

In the Middle East, women are experiencing higher rates of blindness than men in countries where The Fred Hollows Foundation works. In Palestine, for example, women make up 70% of blind people aged 50 years or older.

Blindness can hamper a woman's ability to access education, generate income, or perform day-to-day activities. It can deny women in low- and middle-income countries their social inclusion, participation, and voice as well as an individual's independence, choice, and autonomy.

Barriers to accessing eye healthcare services vary from one country to another. They are created by biological reasons, misconceptions, traditional gender roles, and financial, social and cultural factors.

Implementing a gender equity and mainstreaming approach is a must to achieve equitable access for men and women, but also close the gender gap in eye health. In countries like Pakistan, women often do not know about the eyecare services available or may not have someone to accompany her to the clinic. Taking services to the doorstep of women can help them to receive the care they need, especially in rural and remote areas.

The gender of eye healthcare workers can also be a critical factor in influencing decision making among female patients to accept or decline treatment

Poverty

Almost 90% of women who are blind are living in poverty. Poverty remains a cause and effect for eye health patients as they are not able to access eye care. Community-based service delivery models can tackle the financial barrier and ensure women can access free or low-cost eye care.

Men are our allies and can help to support women who lack decision-making power on their own health, as well as their financial needs and literacy. The Foundation encourages husbands, fathers, religious leaders, politicians, and female health workers to join its efforts in raising women's awareness about avoidable blindness, promoting eye health services, and encouraging them to seek treatment.

Pandemic

The coronavirus pandemic has placed enormous burdens on healthcare systems. The negative impact has extended to people with pre-existing conditions, such as patients living with eye diseases like cataracts. It has severely restricted patients' ability to see ophthalmologists, caused them to miss follow-up appointments, or receive treat-

ments. In Palestine and Pakistan, more than 68,000 eye patients could not access services at our local partner hospitals.

To ensure eye care patients are not left behind – especially elderly women and disabled people – telehealth has been introduced to our projects in Pakistan, Nepal, and Bangladesh. Telehealth allows women living with vision impairment to receive eye care without being physically at the health provider. Women could continue accessing diagnostics and treatment services from health providers despite the pandemic and geographical challenges.

The pandemic has also affected the global economic system. As a result, millions of people's livelihoods have been impacted by this economic crisis and added more financial pressure on marginalized communities including women and disabled people, especially in low resource settings.

We have to ensure patients can access free or low-cost packages of preventions, interventions, treatments, and management. These locally-based packages are crucial to create sustainable change in eye health during pandemic times.

The burden of this global pandemic did not stop at the health-system level, but also extended to healthcare workers. It is very important to look after our frontline healthcare workers, especially women who are stressed at work and home.

Gender

We must ensure strong gender analysis informs the design of all new programmes, and we work to ensure sex disaggregated data is collected, analysed and used to inform programme management, planning and advocacy.

Projects should be designed by looking at health systems with strengthening and sustainability approach and not a vertical standalone activity. This requires collaboration between programmes, advocacy, research teams and local partners who can help maximise sustainable efforts to reduce gender inequity in eye health. Teams ensure they are delivering evidence-based programming, policy, and advocacy, implementing projects which are contextually appropriate, optimizing the use of existing local resources, and evaluating impact through a gender-responsive framework.

Barriers to eye care for women cannot be ignored and should be identified, addressed, and removed to ensure no-one is left behind.

Eye heath actors must develop locally-based solutions and ensure integration between programmes, advocacy and medical research to achieve both gender equity and sustainable efforts to end avoidable blindness. MEH

The Fred Hollows Foundation

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The cost per usage is comparable to a disposable cloth.

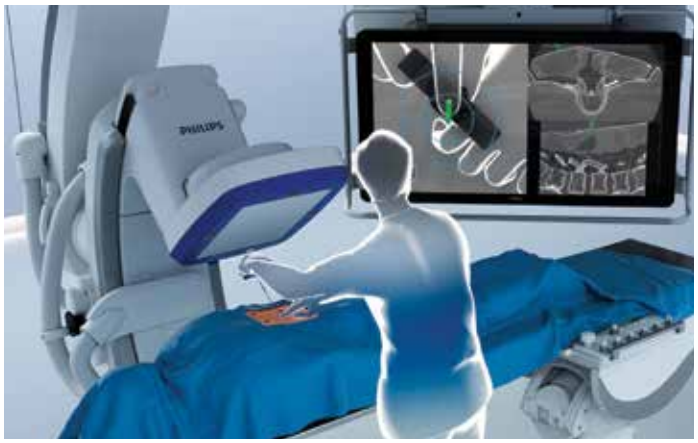
The beautiful and comfortable gloves are the latest addition to this line. They are washable at least 30 times. They provide protection to users even in the most contaminated areas.

All products are PPE labelled. They have the CE mark and have undergone testing according to strict European standards.

- For more information, visit: *www.pastelli.com*

On the pulse

Philips introduces ClarifEye Augmented Reality Surgical Navigation for spinal procedures



Philips has introduced ClarifEye Augmented Reality Surgical Navigation, an industry-first solution to advance minimally-invasive spine procedures in the Hybrid Operating Room.

By combining superb 2D and 3D visualizations at low X-ray dose with 3D augmented reality (AR), the unique solution provides live intra-operative visual feedback to support accurate placement of pedicle screws during spinal fusion procedures.

Four high-resolution optical cameras are used to augment the surgical field with 3D cone-beam CT imaging, without the need for additional X-ray. The system combines the view of the surgical field with the internal 3D view of the patient to construct a 3D augmented-reality view of the patient's external and internal anatomy. Consistent tracking of the patient is ensured by video tracking of non-invasive markers placed on the skin. The system then visualizes the tip of the ClarifEye Needle as it is navigated along the planned path in the spine.

The solution is fully integrated into the Philips Azurion image-guided therapy platform, supporting efficient workflow with intra-procedural navigation and verification for accurate screw placement and reducing the need for post-operative CT scans.

By taking a minimally invasive approach to spine surgery, patients can benefit from reduced postoperative pain, shortened hospital stays, reduced blood loss, and minimized soft tissue damage and scar tissue. In addition, the intra-operative image guidance provided by solutions such as ClarifEye increases clinical accuracy, with patients subject to fewer revision surgeries compared to the current standard of care.

"In spine surgery, when you change your approach to a minimally invasive one, you also have to change the way you operate because you need another way to see inside the spine," said Dr Pietro Scarone, Neurosurgeon at Ente Ospedaliero Cantonale in Lugano, Switzerland. "With ClarifEye, the technology adapts to the needs of the surgeon, rather than the surgeon adapting to the requirements of the technology."

- For information, see this YouTube video. *https://youtu.be/TwZGT1KGvq4*

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Liver cells keep synchrony without master clock

Circadian clocks, which regulate the metabolic functions of all living beings over a period of about 24 hours, are one of the most fundamental biological mechanisms. In humans, their disruption is the cause of many metabolic diseases such as diabetes or serious liver diseases. Although scientists have been studying this mechanism for many years, little is known about how it works. Thanks to an observation tool based on bioluminescence, a research team from the University of Geneva (UNIGE) were able to demonstrate that cells that compose a particular organ can be in-phase, even in the absence of the central brain clock or of any other clocks in the body. Indeed, the scientists managed to restore circadian function in the liver in completely arrhythmic mice, demonstrating that neurons are not unique in their ability to coordinate. Results are published in *Gene and Development*.

For a long time, the scientific community considered that circadian rhythms were entirely controlled by a central clock located in the brain, before discovering, a few years ago, the existence in all cells of the body of a small molecular clock.

"Nevertheless, the brain clock was deemed indispensable for the synchronization of all peripheral clocks," said Ueli Schibler, honorary professor at the UNIGE Faculty of Science, who initiated the work.

Flore Sinturel, a researcher at the Department of Medicine of UNIGE Faculty of Medicine and first author of this work, explained: "Usual research tools did not allow us to explore the validity of this hypothesis. Indeed, to do so, we must be able to follow in real time, over a relatively long period of time, the expression of the circadian genes of an animal with or without a functional brain clock."

Bioluminescence

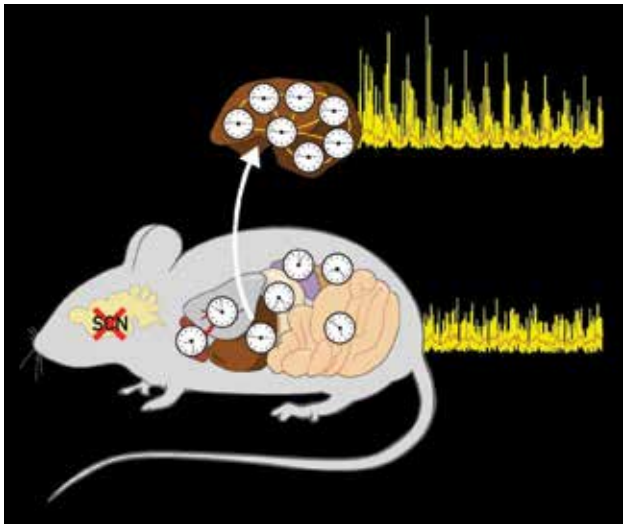
As early as 2013, Professor Schibler's team developed a completely new technology, now commercially available , which makes it possible to monitor the activity of a specific organ and the circadian rhythms that control it. "We were inspired by the principle of bioluminescence that can be observed in fireflies, for example," he explained. "Our mice carry a circadian reporter gene that produces an enzyme, luciferase. We then add luciferin to their drinking water, a substance which, when oxidized by the luciferase, causes photon emission." Light is then captured by a photomultiplier that records the number of photons emitted per minute and thus detects the expression of the circadian reporter gene over time.

Liver clock cells

After the central clock was removed, scientists observed that all the clocks in the body are in different phases. However, at the level of a single organ – the liver in this case – the mice retain a robust and coordinated circadian rhythmicity. So, while the central clock can synchronize all the organs in the same phase, the cells communicate enough to maintain a coordinated rhythmicity within a single organ. "While it was thought that only neurons had strong enough connections to ensure this circadian coordination, we are now demonstrating that this is not the case," said Sinturel. "This puts the singularity of the central clock into perspective."

The scientists then confirmed their discovery: in arrhythmic mice, i.e. mice with no circadian clocks whatsoever, the researchers succeeded in restoring the expression of rhythmicity in the liver alone, without touching the other organs.

"This allowed us to show that a clock restored in one organ works and has rhythms, even in the absence of all the other clocks in the body," she explained.



Mice without a brain clock lose the synchronisation between the different organs, as shown in the bioluminescence profile (right). In the liver, however, synchronisation is maintained.

They now want to understand how these cells stay in the same phase when they are not receiving any information, either from the brain or from other external signals. Their hypothesis? The existence of a form of coupling, in the form of an exchange of molecules between these different cells.

Reference

Circadian hepatocyte clocks keep synchrony in the absence of a master pacemaker in the suprachiasmatic nucleus or other extrahepatic clocks. *Gene and Development*.
doi: *https://doi.org/10.1101/gad.346460.120*

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