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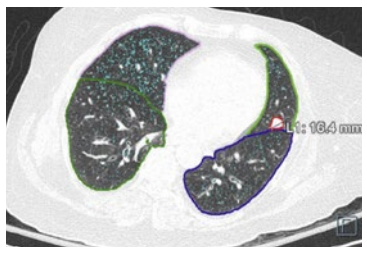

Vaccine hesitancy threatens global health

Measles cases are rising worldwide. Mark Nicholls reports that a trend of falling public trust in vaccines is alarming health officials. The World Health Organisation (WHO) now lists vaccine hesitancy as one of the top 10 threats to global health. The UK's Wellcome Trust 2018 Global Monitor – a survey of some 140,000 people in over 140 countries – highlighted regions where confidence in vaccinations is lowest.

Worldwide, 79% of people agree that vaccines are safe and 84% agree that they are effective. Bangladesh and Rwanda have the strongest confidence in vaccines with almost all people in both countries agreeing vaccines are safe, effective and important for children to have. However, around a fifth of people in Europe either disagree or are unsure of whether vaccines are safe. The lowest confidence levels in relation to vaccines are in Western Europe where 22% of people disagree that vaccines are safe; in Eastern Europe 17% disagree that vaccines are effective. France has the lowest levels of trust in vaccines globally: a third of its inhabitants disagree that vaccines are safe and 10% disagree that they are important for children to have.

Yet, measles is a disease many parents believe to be under control. Contradictory are recent data that suggest a rise in measles cases, combined with a fall in vaccinations. Thus health authorities in Europe, the USA and beyond are increasingly concerned that the condition is undergoing a resurgence and health services are urging parents to have their children vaccinated against what remains a serious – and still potentially deadly and highly-infectious – viral illness.

Some nations are also exploring and implementing more extreme measures in an attempt to halt the increase, such as fining parents, or making vaccination compulsory.

Public Health England (PHE) recently issued a measles, mumps and rubella (MMR) vaccination call following high numbers of measles cases, which followed UK figures from the first quarter of 2019 showing 231 confirmed cases of measles. In the final quarter of 2018, 94.9% of eligible children aged five received the first dose of MMR (to achieve herd immunity for measles, at least 90-95% of the population should be fully protected), though second dose coverage was 87.4%

Less than 95 % coverage can lead to outbreaks

'Anything less than 95% [vaccination] coverage can lead to outbreaks and that's what we're seeing,' explained Imran Khan, from the Wellcome Trust. The overwhelming scientific evidence remains that vaccination is the best defence against infections,

Source: Shutterstock/Zerbor

such as measles but people avoiding vaccines, often as a result of misinformation online, or complacency, are possible causes of a resurgence in the condition. Concerns around vaccines, such as in France about a pandemic influenza vaccine and in the UK where research (since discredited) suggested a link between the MMR inoculation and autism, have had an impact, as has the rising profile of anti-vaccination movements.

People living in several higher-income regions were among the least certain about vaccine safety and mistrust of doctors was also seen as a factor in some countries, though a PHE survey highlights that healthcare professionals remain the most trusted source of information on immunisation, while social media ranks bottom of the table.

'Vaccine hesitancy has the potential, at least in some places, to really hinder the very real progress the world has made in controlling vaccine-preventable diseases. Any resurgence we see in these diseases are an unacceptable step backwards,' warned WHO immunisation expert Dr Ann Lindstrand.

The WHO reports that vaccination resulted in an 80% drop in measles deaths between 2000 and 2017 worldwide. Before the introduction of vaccine in 1963, measles caused an estimated 2.6 million deaths annually. By 2000 it was 545,000 annual deaths, but there were still 110,000 measles deaths globally in 2017, mostly among children under five, despite lower-cost vaccine availability.

Large outbreaks in various countries

The European Vaccine Action Plan (2015-2020) aims to eliminate measles and rubella, with 95% of each country's population to be immunised. Yet the surge in cases in 2018 – which followed a year in which the European Region achieved its highest ever estimated coverage for the second dose of measles vaccination – continues to be alarming.

'The picture for 2018 makes it clear that the current pace of progress in raising immunisation rates will be insufficient to stop measles circulation,' Dr Zsuzsanna Jakab, WHO Regional Director for Europe, pointed out. 'While data indicates exceptionally high immunisation coverage at regional level, they also reflect a record number affected and killed by the disease. This means that gaps at local level still offer an open door to the virus…we must do more and do it better to protect each and every person from diseases that can be easily avoided.'

Fresh data shows cases rose in almost every world region, with 30% more cases in 2017 than 2016.

In the first two months of 2019 there were 34,300 cases reported in 42 countries of the WHO European region and 13 deaths as some countries step up the fight against the disease.

In France, where in the first quarter of 2019 there were 561 cases of measles, the government has added eight more compulsory vaccinations to the three children in the country already receive while in Italy - where 76% agreed vaccines were safe – schools are now allowed to ban unvaccinated children. Germany, which saw 170 cases in the first two months of this year, is looking at fines of 2,500 euros for parents who refuse to get their children vaccinated. (There are currently 360,000 unvaccinated children in the German school system.)

Ukraine had the highest number of measles cases in Europe last year (53,218); only half the population agreed vaccines were effective. America has also experienced its biggest measles outbreak for some time with almost 1,000 cases so far this year.

The UK's PHE is advising citizens to check their MMR vaccinations – particularly when travelling to countries where the European Centre for Disease Prevention and control (ECDC) reports current large measles outbreaks, such as France, Lithuania, Poland, Romania, Bulgaria and Germany – as many cases in England have been linked to importations from Europe. 'With ongoing measles outbreaks happening across Europe, those planning to travel should check with their GP,' warned Dr Mary Ramsay, Public Health England's Head of Immunisation.

The UK's effective MMR vaccination programme

Measles remains uncommon in the UK. The MMR vaccine is given by the UK's National Health Service (NHS) as a single injection to babies as part of their routine vaccination schedule, usually within a month of their first birthday. A second vaccination is given just before those children start school.

'We are very lucky England has one of the most comprehensive [vaccination] programmes in the world and it's really great to see that parents trust our programme and most children benefit from this offer,' Ramsay explained, adding that all websites and social media platforms should ensure accurate health information, and that vaccine reminders should be sent out, and GP appointments easily made. 'Measles can kill and it is incredibly easy to catch,' Ramsay warned, 'especially if you are not vaccinated.

Dr Mary Ramsay is Head of Immunisation at Public Health England and leads national surveillance of vaccine preventable diseases and provides expert advice and support to a range of professionals and organisations that contribute to public health, in England and overseas. She has acted as a temporary advisor to WHO and advises the ECDC on surveillance and epidemiology of vaccine preventable diseases. Her research interests involve establishing the potential role for new vaccines.

Dr Zsuzsanna Jakab became a WHO Regional Director in February 2010 and in 2015 was appointed for a second term. In March 2019, she was appointed Deputy Director-General of WHO with a portfolio that includes WHO's technical programmes for universal health coverage, communicable and noncommunicable diseases, healthier populations and antimicrobial resistance. She previously served as the founding Director of the ECDC and earlier was State Secretary at the Hungarian Ministry of Health, Social and Family Affairs.

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A truly smart children's hospital

Tools: tracing, tracking, relocati

In a busy hospital, thousands of devices and equipment are on the move every hour of every day. Beds, blood pressure monitors, wheelchairs, or infusion pumps can be taken to different locations and, at times, even 'lost'. Keeping track of vital tools is a challenge, particularly given the massive throughput of patients and staff shift changes.

However, innovative tracking systems are evolving that not only identify where items are, but they also prompt for redelivery to where they are next required.

Fujitsu beacons and tags

The Dutch Children's Hospital in the Netherlands gave Fujitsu and partners the opportunity to provide a unique solution to track and trace hospital assets. This involves mobile tags, sensors and anchor nodes that automatically connect with one another to keep track of assets.

The initiative is part of a broader project to improve efficiency and quality of care throughout the hospital. Dennis van Doorn, Marketing Manager Wireless Solutions at Fujitsu, explained how Fujitsu is working on these projects.

From the first successful proof-of-concept pilot for tracing and tracking, a follow-up pilot is underway, with equipment connected through battery-powered asset tags that send a signal to a mesh network.

As the mesh network can also dovetail with smart lighting systems, further opportunities were suggested. This progressed when it emerged that the Dutch Hospital was preparing a project to upgrade existing lighting to sustainable LED smart lighting – where, as part of the Fujitsu connectivity solution, that system can be interconnected with the other solutions offered.

The team began to imagine a smart light system throughout the hospital, connected wirelessly with mesh technology, sensors and asset tags. 'By rolling out the whole infrastructure of lights, we can do asset tracking throughout the whole building very easily,' van Doorn said. 'From two different groups in the Dutch Hospital – one asking for asset tracking, the other for sustainable lighting – we are now suddenly offering much more.'

Due to renovation work, an empty ward presented an ideal opportunity – test bed location in which to install the technology and demonstrate its capabilities without impacting on care and other work.

The total solution also includes decision-making software and dashboards for task management within the hospital; IoT Solutions can also benefit the patient and visitor experience – an indoor navigation solution has been added to guide and inform patients and visitors. The solution has been expanded to include energy-harvesting wireless switches that can be addressed to any action, such as a request for cleaning, a call nurse, etc.

'We are feeding out asset tracking information and location information and visualising medical equipment on the floor plan for nurses and other staff,' van Doorn said. 'If stock levels in a certain area gets too low there will be a notification on the dashboard and staff mobile devices.'

With the proof-of-concept under way, four further pilot projects are being established at the hospital. One involves tracking the whereabouts of wheelchairs, others are on the geriatric and gynaecology wards to keep track of beds, infusion pumps and blood pressure measurement devices, while a further project is in a 'smart operation theatre'.

Dashboard and inventory control software

'There, we are going to connect occupancy sensors to the network, to see if we can save money on occupancy of operation rooms,' van Doorn explained. 'If nobody is detected, the lights and ventilation should not be on. We're going to use sensor data combined with the operation schedule, to see if we can make it more efficient.'

A further proposed study will look at staff movements in intensive care, to remove unnecessary distractions

AI in diagnostics

Learn like a human, deduce like a r

Artificial Intelligence (AI) is like a huge blanket that can cover anything from innocuous chess computers to robots which, depending on your viewpoint, could save, oppress or obliterate humanity. However, not every jar labelled AI contains AI. So what is intelligence and can it be created artificially, synthesised like a nature-identical flavouring substance? At the Siemens Diagnostik Campus, Dr Martin Hirsch, co-founder and CSO of Ada Health GmbH, explored why the term artificial intelligence is frequently misunderstood and why, nevertheless, this technology has the potential to be a major driver in healthcare, Daniela Zimmermann reports.

For some people, machine learning is the computer equivalent of intelligence, but Dr Martin Hirsch begs to differ. 'For me, first and foremost, intelligence is the ability to generate sensible behaviour in an entirely new situation. An algorithm that iterates a procedure thousands of times and then deduces certain rules from these runs is not necessarily intelligent.' In other words: intelligence is the ability to generate hypotheses from existing knowledge and, in a next step, to recognise possible courses of action.

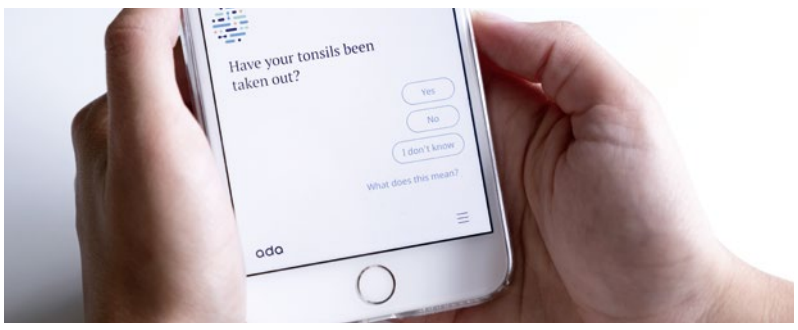
Co-founder and Chief Scientific Officer **Martin Hirsch** PhD qualified in Neuroscience and has a Diploma in Physiology. A medical researcher turned serial entrepreneur; Dr Hirsch shifted from theory to innovation after publishing his work on nerve modeling in the scientific journal Nature. His first venture was a nerve modeling program that saved thousands of animals from lab testing. He developed the first version of Ada for doctors and continues to shape the way Ada learns today. Hirsch is a grandson of the celebrated Nobel Laureate Werner Heisenberg.

While a computer requires innumerable data sets to master a certain procedure reliably, humans in many cases need but a single illustrative example to recognise and understand complex relationships. 'That's due to our ability to abstract,' Hirsch explains. While building knowledge in humans may take much longer than feeding an algorithm with data sets, the brain of a physician, for example, will acquire a deep understanding that can offer a sound solution even in unfamiliar cases.

Pattern recognition – all the rage in medical applications – might be sufficient to provide a working hypothesis, but never a reliable diagnosis. A pattern recognised by the computer may indeed be due to patient physiology, but it may also be due to poor data, such as image artefacts. 'When building a decision support system, therefore, we shouldn't start from square one, but build upon validated scientific knowledge,' the neuroscientist underlines. Ideally, he says, we use existing knowledge and incorporate insights from pattern recognition. This approach is rather similar to the "human model" where junior physicians first acquire knowledge during their medical school studies and later expand and adapt this knowledge with each day of practical experience.

'How did you figure this out?'

Ada, an AI-based platform developed at Hirsch's eponymous company, works pretty much according to this pattern. It analyses certain parameters, weighs them and generates a hypothesis from these data, accompanied by a probability score for the validity of the hypothesis. 'This includes collecting positive and negative evidence, very much like during a differential diagnosis. Ada tries to compare and contrast similar pathologies to differentiate and exclude.' This procedure is meant to make the 'thought process' of the algorithm understandable for the human brain. 'Transparency is crucial,' according to Hirsch, because 'AI systems will only be able to prevail in a hospital and healthcare system if the machine can explain why it arrived at a certain conclusion.'



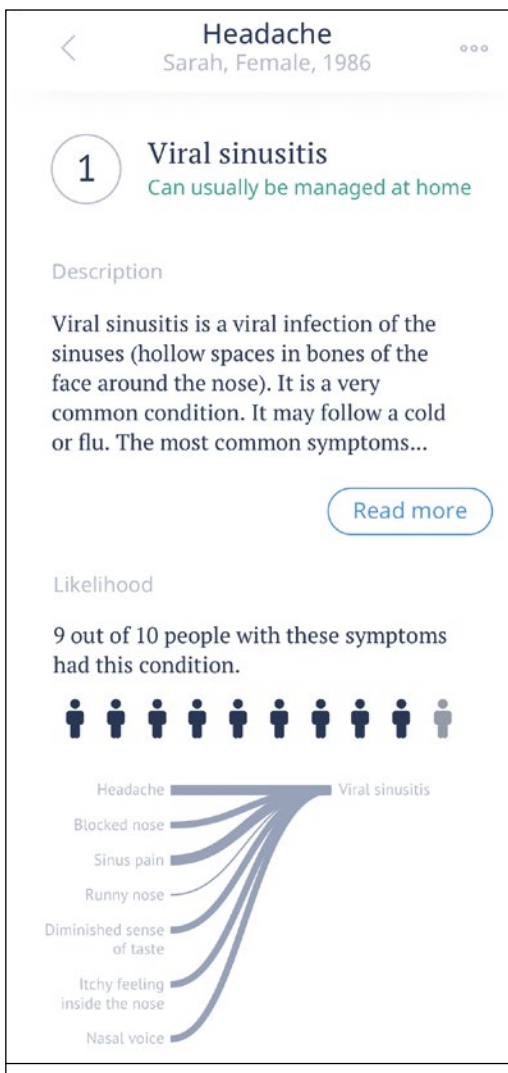
The AI-based platform ADA analyses certain parameters, e.g. if the tonsils have been taken out. The system covers 18,000 disease codes from ICD-10, like viral sinusitis

Currently, the system covers 18,000 disease codes from ICD-10 – a number far beyond the capacities of a human physician. 'Physicians can't know the entire range of lab diagnostics, since the human brain is unable to process this degree of complexity,' Hirsch said. Even if the appropriate test is selected, the physician might draw the wrong conclusions from results. This is where AI can help. A recent study published in the Orphanet Journal of Rare Diseases found that, in 54% of cases investigated, AI could indicate a diagnosis faster than a human physician.

Chatbot anamnesis

While many physicians are rather wary of chatbots, patients appear to have fewer reservations, as the experience with Ada shows. The patients describe their symptoms to a chatbot, just as they do during a conventional anamnesis, and AI algorithms draw a working hypothesis – a preliminary diagnosis – from these data. 'To date, we have delivered over 12 million such assessments to more than seven million users,' says Hirsch, who is convinced that his system meets a real need. The chatbot offers patients something they often miss in their doctor's office: time.

The AI assistant is not under pressure and asks as many questions as necessary to be able to arrive at a conclusion. Moreover, many people find it easier to talk about delicate personal health issues when the counterpart is a machine, rather than a human being. 'The future healthcare pathway will not start in the physician's waiting room, but in the patient's palm. People really do want to find out more about their conditions and possible therapies and this, in my opinion, is the point where AI meets the patients,' Hirsch says. However, he



ing – no problem

and thereby allow patients to fully focus on recovery.

Future developments

'We know it works and are already thinking further ahead with partners to provide an off-the-shelf solution worldwide, because all hospitals are facing the same challenges.'

While several wi-fi based or radio frequency identification (RFID) track and trace systems exist, van Doorn believes the Fujitsu-led approach offers more flexibility to hospitals due to the firm's ability to install a battery-powered network 'within a few hours'. Additionally, hospitals upgrading to more sustainable lighting systems presents a further opportunity to install networks that dovetail with trace and track technology, he added.

'With the flick of switch we can make a whole network work as an asset tracking network,' he said. Sensors can enable smart light functions to act as an 'eye' to locate an asset and, for example, translate a call for a bed into action for its delivery to a specific ward.

As hospitals face greater pressures to increase efficiency, harnessing technology to trace, track, locate and deliver assets will not only benefit workflow but far more.

Dutchman **Dennis van Doorn**, Marketing Manager for IoT Connectivity, Fujitsu Components Europe B.V., explains his involvement: 'Roughly eleven years ago my education, experience and my passion for gadgets and their development, turned into a business challenge when Fujitsu Components added Wireless Modules to their product portfolio. The Internet of Things has taken a great step forward since we started the development of wireless solutions within Fujitsu. These developments have inspired and convinced me, that one product by itself will not be the solution to the complexity of IoT integration, but the right combination of building blocks is. This evolves from bringing people together and growing networks of highly specialised knowledge. The future of IoT integration, taking the expected massive number of devices and how to handle these complexities,' he adds, 'intrigues and challenges me.'

machine

emphasises that such a system cannot and will not replace the human physician. These AI developments open many new doors: 'Such applications can help us structure patient flows in a sensible way,' Hirsch says, since the recommendations offered by the system can stop people from unnecessary visits to their GP or, even more importantly, to a hospital A&E.

Moreover, the applications have enormous predictive potential, according to Hirsch. When, in early 2019, the number of measles cases in the USA increased massively, AI had seen it coming – six weeks earlier – simply because an unusual high number of users had talked to the chatbots about measles symptoms. Hirsch: 'Symptom-based epidemiology offers many new possibilities.'

Two further promising areas for AI in healthcare are risk assessment and prevention, Hirsch points out. Even genetic factors can be considered: 'Genetic data is nothing but probability data. Why then should AI diagnostics, which is also based on probability, not use it?' Hirsch asks. This means that two patients with identical symptoms might receive different treatments if a genetic test indicates that one of the two has a higher probability for a certain underlying disease.

In developing countries, with few specialist physicians, AI-based diagnostics could help GPs to treat patients who present with a complex symptom landscape. Even in very basic exams, the developers are believe AI-based applications can contribute significantly to primary healthcare.

[Orphanet Journal of Rare Diseases [https://doi.org/10.1186/s13023-019-1040-6]

Everyone's DNA is recorded for disease risks

Genetic analysis for all Estonians

Report: Daniela Zimmermann

When it comes to genetics, Estonia has long been considered a trailblazer, as the ambitious Estonian Genome Project (Eesti Geenivaramu) shows. Its objective is to test the genome of each and every citizen for the risk of diseases. Where risks are detected, testing is followed up with information, prevention and, where appropriate, treatment. Dr Jaanus Pikani, one of the initiators, talks about the initial difficulties which the genome project encountered and about its potential for Estonian – and possibly worldwide – healthcare.

When the project was launched in 2000, various hurdles had to be overcome. Pikani recalls: 'Most people were worried about data protection – and this continues to be the case.' Therefore, the security standards to protect the genome data from misuse were high from the very beginning. Not everything worked well financially, either. Whilst the project (a private-non-profit partnership between the Estonian government with a company called EGeen) initially benefited from the hype caused by reports of success in the International Human Genome Project (HGP), both investors' interest and support markedly waned over time. The project, then handed to the public domain, is now run by the University of Tartu.


Source: shutterstock/nednapa

150,000 data set with an upward tendency

Meanwhile the project now comprises the data sets from more than 150,000 people; information such as gender, age, height and weight is stored as well as data on medically relevant factors, such as dietary habits, exercise and smoking as well as individual and family medical history. At the core of the examination is a blood test used to extract DNA. Participants' leucocytes are also cryo-conserved for later use.

There is a good reason for this foresight, explains Pikani: 'When we started collecting data for the biobank there was no affordable technology we could have used to carry out genotyping or sequencing.' However, advances in genetic research now facilitate the evaluation of the data collated.

Genetic early warning system

These datasets not only drive science but also benefit the donors themselves. 'If a higher risk of developing cancer is found in the genome, for instance, the case is passed to an oncologist and targeted sequencing is carried out.' This way, in 5-10 years, preventive measures such as mammography screening, could become obsolete, Pikani believes. 'This eliminates the exposure to radiation during an examination, the number of false-positive results will fall, and it also allows us to target younger women who would not usually participate in screening.'

A further aspect concerns pharmacogenomics: 'A small percentage – around 2% of the population – metabolise drugs either much faster or slower than the rest,' Pikani underlines. 'This is often evident from the genes. If such a marker is found, prescriptions must be adapted to avoid under- or overdosing.' In Estonia, where prescriptions are administered electronically, doctors could also automatically be warned about any such particularities with their patients.

One genome, to take away please!

Participants of a pilot group can even have their genomic data handed over to them so that, if they wish, they can pass it on for analysis to another health service provider. However, within the pilot project, the genome data for all participants will be screened to find risk variants, and if increased risk is detected the participants will be invited for further investigations. In this case, referral pathways and data exchange between the Genome Project, hospitals and family doctors will be elaborated and tested. 'We want to find out how this data can be handled in the healthcare system.' One tricky area is how to handle hereditary diseases, says Pikani: 'Biobank participants have agreed to the testing – but what about their relatives? Are we allowed to point towards existing risks, or must we, even? We must think very carefully about the ethical consequences.'

Pikani sees a large potential in the genome project: 'Biomarkers such as BRCA2 can predict the occurrence of certain diseases with high probability – in this case, breast cancer. There are also similar markers for cardiovascular diseases.' The early detection of such risks can be utilised for effective prevention. 'Obviously there are some who won't take the results seriously. But, for many, the knowledge that they are at double or even three times higher risk of suffering a heart attack is a strong enough incentive to do something about obesity or tobacco consumption.'

Doctors must learn to read

Until a comprehensive introduction is achieved, family doctors will need to receive thorough training in how to handle genomic data to ensure that they can interpret it correctly. The development of a technological infrastructure to handle the data in a lawful manner is also planned. Funding from the European Structural Funds is to be made available for this.

Pikani hopes to capture the entire Estonian population in the near future: 'If we gain 100,000 citizens a year, we will have achieved this objective in only ten years.' As the project is publicly financed, the population must be convinced. 'The procedure is becoming increasingly more economic, particularly in relation to the possible treatment costs, which can run easily to several thousand euros in some cases.'

Many nations will be watching the genome project with great interest, but it is no coincidence that Estonia is a trailblazer. 'We are very open-minded towards new technologies; we have been able to vote electronically for the last 15 years, for instance,' Pikani points out. The fact that the entire population is only 1.3 million also favours the implementation of a national project. If it succeeds in Estonia, Pikani foresees implementation in other countries, and on a larger scale, may well become an option.

Dr Jaanus Pikani is chairman of the Tartu Biotechnology Park and the Life Science-, Bio- and Health-Tech-Meta-Cluster Organisation ScanBalt. As an entrepreneur and health advisor he also works for the World Bank and the WHO. Dr Pikani is one of the initiators of the Estonian Genome Project.

Endoprosthetic patients face high risk of infection

Clinical practice needs realignment

Periprosthetic infections are widely underestimated, despite the fact that they can have a mortal outcome as cancer, for example. Particular attention must be paid here to patients with a high risk of infection – which might be caused through pre-existing conditions or sources of infection already present in the body. How can this risk group be better addressed in clinical practice? What methods are available to prevent periprosthetic infections or, at least, to detect and treat them more quickly?

Biofilm control is the top priority

Infections break out sooner or later in 5-10% of all implants placed. Millions of patients are affected, as just in 2017 more than 117 million implants were inserted worldwide, according to Professor Andrej Trampuz, Charité University Hospital Berlin and founder of the Pro-Implant Foundation. The number of implants inserted, as well as the number of infections diagnosed, is rising steadily. In the USA, the number of periprosthetic infections of hip and knee implants increased almost sixfold between 2001 and 2020; the associated costs for the healthcare system are set to rise from just under US$400 million (2001) to an estimated US$1.6 billion in 2020.

Trampuz sees the key to solving the problem in the prevention or elimination of the so-called biofilms formed by bacteria on the surface of implants, serving as protection for pathogens and making them hardly reachable by the immune system and drugs. The interdisciplinary cooperation of surgeons and infectiologists, as well as the closely meshed coordination of the administration of antibiotics, surgical measures and diagnostics, is indispensable.

Periprosthetic infections: a complex problem worldwide

The experience of the Pro-Implant Foundation and its consultation portal for the treatment of implant-associated infections confirm that periprosthetic infections are a sensitive issue worldwide. Since 2018, doctors internationally have taken advantage of the portal in over 3,000 cases of infection in implants. Based on the cases submitted, important conclusions can be drawn about the failure of periprosthetic infection treatment.

On the one hand, periprosthetic infections often go undiagnosed or are diagnosed too late. This is partly due to the limited number and performance of diagnostic tools available in this area. However, it is often neglected to establish a sound understanding of the patient's pathogens prior to surgery.

On the other hand, it is often not distinguished whether the infection is acute or chronic. However, this differentiation has a considerable influence on the required treatment regimen, according to Trampuz. Infections that are difficult to treat due to resistant biofilm-forming pathogens (e.g. candida, rifampicin-resistant staphylococci) are particularly problematic. The aim must be to determine precisely the treatment regimen that not only considers the type of infection, but also requires the least invasive intervention while providing the best functional results.

As an additional problem area, Trampuz mentions overlooking low-threshold infections. There are different definitions (MSIS, IDSA), each with different criteria, but both can lead to infections or pathogens not being detected. Trampuz sees the identification of identical microorganisms from at least two different cultures as the most important common factor. A new, improved definition (EBJIS) is currently being discussed.

A further challenge lies in proving the systemic origin of an infection. There are still 20% of all periprosthetic infections caused by the transmission of pathogens from a distant organ (e.g. oral cavity) via the patient's bloodstream.

Furthermore, often systemic antibiotics are not used specifically and for long enough. That is why Trampuz advises against the previously propagated suspension of antibiotics during two-stage prosthesis replacement and favours longer, continuous administration. Antibiotics that work against biofilms, such as ciprofloxacin or ampicillin plus gentamicin, are especially helpful here.

Local antibiotics in spacers and bone cement, which – ideally combined with systemic antibiotics – are used for both primary interventions and revisions, play a decisive role in fighting periprosthetic infections, according to Trampuz. The advantage of locally applied antibiotics lies in the fact that they are specifically released on site in significantly higher concentrations (10-100 times higher) than with systemic administration. At the same time, the entire organism is spared, as the local use of antibiotics only has a slight systemic effect.

Misjudgements – the lurking danger

All of the above areas must be covered in clinical practice. Even a single misjudgement, e.g. overlooking a low-threshold infection, or a too short administration of antibiotics, can lead to revisions and complications that are actually avoidable. There is still potential in clinical practice to expand collaboration within multidisciplinary teams in order to address periprosthetic infections more systematically and comprehensively in the future.

*Source: Heraeus Medical satellite symposium 'Arthroplasty patients with high risk for infection – do we need to change our clinical practice?'. EFORT 2019

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A consensus statement published at EuroPCR 2019

Intracoronary imaging advances

Report: Jane MacDougall

Interventional cardiologists have been aware of the value of intracoronary (IC) imaging in clinical practice for more than twenty years. However, recent developments and improvements in modalities and software have enabled huge strides in its range and scope for both diagnostic assessment and in percutaneous coronary interventions. Imaging options now include intravascular ultrasound (IVUS), optical coherence tomography (OCT) and near-infrared spectroscopy. This organic growth has created significant differences in the use of IC imaging across regions and institutions.

Generally speaking, IVUS is the most established IC imaging technique, used in more than 80% of PCI cases in Japan, but OCT the equivalence of which has now been confirmed, is increasing in popularity. In an attempt to homogenise its application, the European Association of Percutaneous Cardiovascular Interventions (EAPCI) has generated frequent consensus statements on its utility, drawing on clinical evidence from imaging studies and best practice experience.

The ESC revascularisation guidelines, published in early May, strengthen the indications for IC imaging by recommendation. In light of these new recommendations there was an official presentation of the consensus statement at EuroPCR and also a training session presented by two of the authors, Thomas W Johnson from Bristol, United Kingdom, and Francesco Prati from Rome, Italy.

Delineating the extent of coronary artery disease

Intracoronary imaging provides an adjunct of information to angiography and, therefore, is invaluable for delineating the extent of coronary artery disease and characterising the severity of atherosclerotic lesion(s), which may appear ambiguous from angiography alone.

Angiography overestimates lumen dimensions and is limited by its two-dimensional view of a three-dimensional structure which, as a consequence, results in poor and/or inaccurate estimations of plaque volume, morphology or lesion severity. All of this information can be more precisely obtained by intravascular imaging, OCT being of particular use in thrombus detection because it can distinguish between red (due to the optical attenuating properties of red blood cells) and white thrombi, the difference between which dictates the choice of pharmacological management.

At a training session at EuroPCR, the role of IC imaging was considered in three areas:

- Defining and optimally treating calcified coronaries: coronary plaques can be classified based on the amount of calcium in a lesion. The presence of segments with partially calcified or calcified plaque has been suggested to have a significant effect on mortality; therefore, the use of intracoronary imaging to assess and guide modification strategies for high-burden calcification is increasing. Calcified plaque is brightly echo-reflective and creates a dense shadow, as well as reverberation markers that appear radially at spaced intervals from the calcified segment. With electronic callipers and computerised planimetry, accurate quantitative measurements can be made at the narrowest cross-section to determine the minimal luminal area (MLA) and diameter and at another 'normal' segment (within 10 mm of the culprit lesion) which is used as a reference for the healthy diameter of the vessel. This allows calculation of the percentage stenosis, plaque area and plaque burden and guides appropriate treatment strategies.
- Understanding the potential of intracoronary imaging to define the aetiology of atherosclerotic ACS and to guide management: determining lesion morphology has direct implications for the treatment strategy to be implemented. Historically, treatment in ACS has been focused on stabilising thin-cap fibroatheroma associated with thrombus formation. However, the widespread use of IC imaging in research, particularly OCT has shown that in one-third of all ACS and one-quarter of STEACS are caused by plaques with an intact fibrous cap, the majority seen as eroded plaques. Identification of this type of plaque means treatment can be tailored to the individual characteristics of the patient's disease. Plaque erosion, characterised by endothelial denudation, tends to occur in younger patients including pre-menopausal women and is associated with active smoking in an absence of traditional factors for heart disease. Generally, its treatment is associated with better outcomes than plaque rupture and if correctly diagnosed can be conservatively treated.

DES stent for practice sessions.

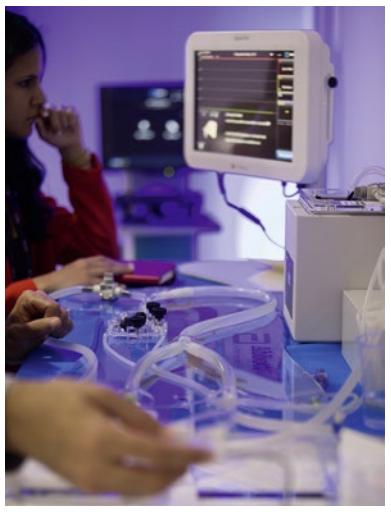
Non-atherosclerotic ACS

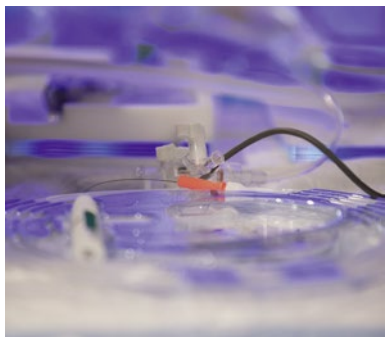
- How to delineate and manage non-atherosclerotic ACS presentations: Historically, IC imaging has concentrated on the use of intracoronary imaging in pre-PCI assessment in patients with acute coronary syndrome (ACS). In the stable population angiographic ambiguity occurs under many circumstances, when there is excessive plaque burden, calcification, old plaque rupture, coronary tortuosity, or aberrant vessel anatomy.

Under those conditions, intracoronary imaging provides clarity, revealing the detail within the vessel. Careful acquisition of angiographic and IC imaging has created a reliable database that facilitates analysis of IC images, however, correct interpretation still requires a considerable level of expertise, training and experience.

Despite being with us for more than 20 years, intracoronary imaging is still pushing forward the boundaries of what can be achieved in interventional cardiology. Newer probes, bluetooth and Wi-Fi connections mean that imaging is an integral part of the Cath lab, used at all stages of intervention.

The rapidly advancing technology brings higher resolution images, faster acquisition times, combined techniques and a mass of data to mine to gain clinical evidence needed to drive the field. given the array of options displayed at EuroPCR, the future of intracoronary imaging-guided PCI is very exciting.





EuroPCR participants enhancing their OCT-guided PCI and physiology assessment techniques in hands-on dummy situations in the Abbott training village.

* Further info: https://www.youtube.com/watch?v=7eP1DAiznNo

Johnson TW et al. Clinical use of intracoronary imaging. Part 2: an expert consensus document of the European Association of Percutaneous Cardiovascular Interventions European Heart Journal. 2019 ;0:1-19

High tissue contrast, spatial detail, complete tissue characterisation

MRI shows cardiac diagnostic value

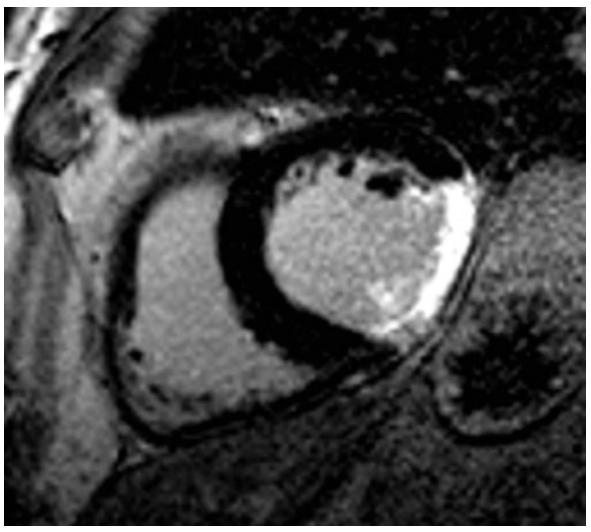
Report: Mark Nicholls

Cardiovascular magnetic resonance (CMR) imaging has become faster, simpler and more widely available in recent years because it has evolved to deliver effective assessment and diagnosis of a range of heart conditions with expanding guideline indications.

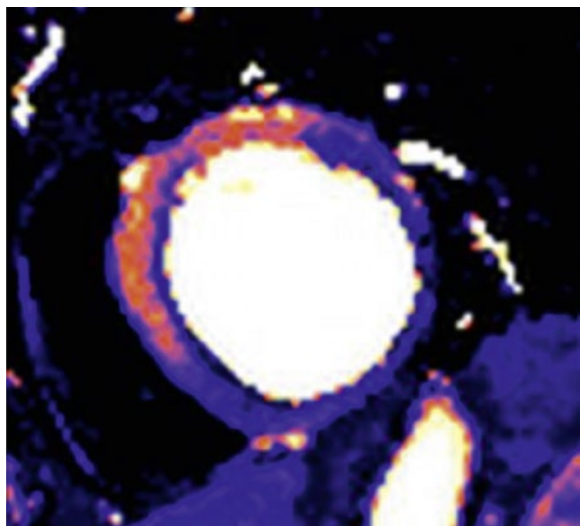
'MRI is the reference test for anatomical imaging of the heart, for quantifying chamber sizes and function,' explains Professor Sven Plein, British Heart Foundation Professor of Cardiovascular Imaging and Professor of Cardiology at the University of Leeds, United Kingdom.

Over recent years, with his Leeds team he has conducted extensive research on MRI – significantly in the cardiac arena – and in particular on the cardiovascular effects of diabetes using MRI and in developing quantitative MRI methods. 'Cardiovascular MRI,' he points out, 'is a non-invasive and safe imaging test with the main benefit of providing high tissue contrast, spatial detail and comprehensive tissue characterisation.

Recent developments in parametric mapping and automated perfusion analysis are continuing to move magnetic resonance imaging from visual analysis to quantitative description of pathology.'



Late gadolinium-enhanced MRI in the mid-ventricular short axis plane showing contrast enhancement in the infero-lateral segment indicative of transmural myocardial infarction



Myocardial perfusion map in the mid-ventricular short axis plane showing reduced myocardial blood flow during adenosine stress in the infero-septal, inferior and lateral segments (blue colours) and normal stress blood flow in the anterior and antero-septal segments (orange-red colours)

MRI vs. CT

Whilst MRI offers a number of benefits over CT, he emphasises that the two modalities should be regarded as complementary rather than competing.

'CT is the method of choice for imaging the coronary arteries, while MRI is most powerful for functional imaging of the myocardium,' Plein adds. 'Of course, CT exposes patients to a small dose of X-ray radiation, while MRI doesn't, and MRI contrast agents are generally safer than CT contrast agents. In practice, however, both tests are increasingly used to replace invasive methods for different indications.

'In congenital heart disease, MRI is the "go-to" test to figure out complicated anatomy, and plan and assess the effectiveness of complex surgery. In children in particular, we need to avoid repeated exposure to X-rays, so we would always aim to use MRI as the first line test.

'Increasingly, cardiologists are using MRI not just to take anatomical pictures, but also to assess tissue composition and tissue characteristics of heart muscle.'

A quantitative colour map

Plein outlines the benefits of para metric mapping as an important area of development and one that delivers a quantitative colour map output that encodes a range of tissue properties such as T1, T2 and T2* times.

'We can map areas and create normal values for these parameters. Increasingly, these quantitative methods are used to describe the composition of the cardiac muscle and its content in terms of fibrotic tissue, fat and water content as well as abnormal loading with, for example, iron in thalassaemia patients,' Plein explains.

After several years of development, myocardial blood flow can now also be measured quantitatively with automated in line methods via MRI. That development – which is important in ischaemia detection – will shift the approach from the subjective observation of an experienced cardiologist assessing dynamic images of heart muscle enhanced by contrast, to a numeric quantification of blood flow from a colour-coded map.

Stress perfusion imaging

'Techniques are now coming onto the market where software generates a colour map that shows the amount of blood flow through the heart muscle at rest and during stress – stress perfusion imaging – and whether there are any abnormalities,' Plein continues. 'These will soon be commercially available, offering another exciting addition to the growing quantitative MRI methodology.'

Magnetic resonance imaging continues to help improve understanding of heart disease. 'MRI provides detailed information about cardiac and vascular function, presence of scar or fibrosis in the heart muscle, fat content, blood flow and much more,' he points out. 'In daily practice MRI is becoming an indispensable test for patients with congenital heart disease, cardiomyopathy and heart failure, ischaemic heart disease and more.

'In research, MRI methods are in development to image a heart's microstructure, visualise complex four-dimensional flow, and heart metabolism.

'This helps to better understand of mechanism of heart failure and other conditions.'

Sven Plein is British Heart Foundation Professor of Cardiovascular Imaging and Professor of Cardiology at the University of Leeds, where he leads a large interdisciplinary research group for development and clinical implementation of imaging methods. Key areas of research are on the cardiovascular effects of diabetes using MRI and in quantitative myocardial blood flow measurements. The professor also heads the Department of Biomedical Imaging Science, in the Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds and is Consultant Cardiologist & Clinical Lead for Cardiovascular Magnetic Resonance at Leeds Teaching Hospitals National Health Service Trust.

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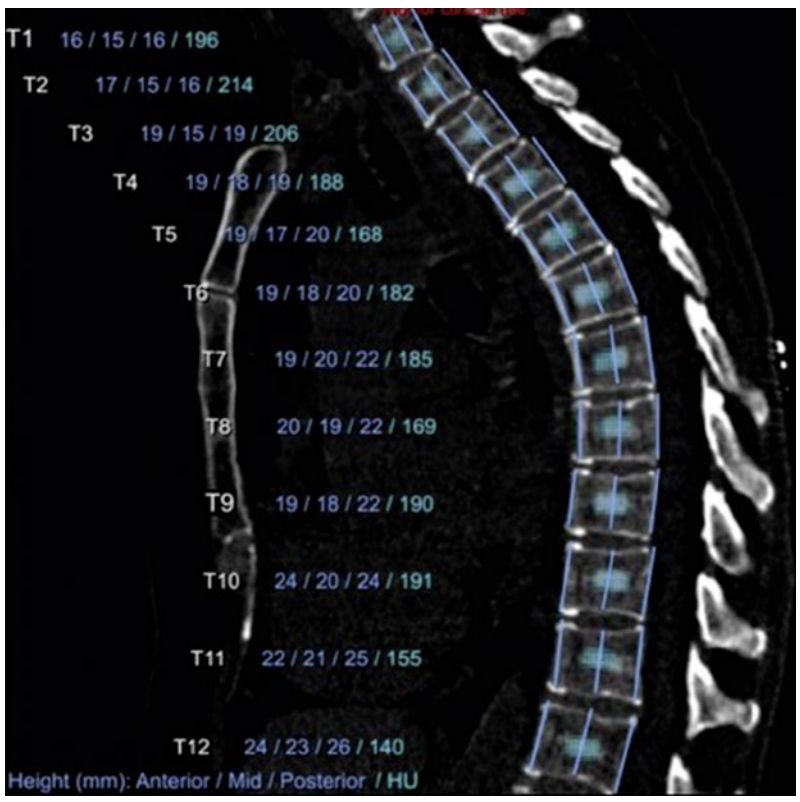
AI opens up boundaries between medical disciplines

AI-based evaluation of chest CT scans allows comprehensive assessment of different organ sections

Uwe Joseph Schoepf, Professor for Radiology, Cardiology and Paediatrics and Director of the Department of Cardiovascular Imaging at the Medical University of South Carolina, discusses areas of application for AI-based radiology with Daniela Zimmermann. The cardiothoracic imaging expert and his team were largely involved in the development and early clinical trials of the Siemens AI-Rad Companion Chest CT, a software package for computed tomography (CT) based on artificial intelligence (AI).

On CT scans the application can distinguish between thoracic organs, such as the heart, lungs, aorta or vertebral bodies, and detect anomalies. Achieving this ability entailed training the software with real clinical cases from Schoepf's department, where the system was being trialled. Those trials were also used to find answers to further diagnostic questions. 'Apart from cardiac problems, such as automatic measuring of the aorta, interdisciplinary aspects, such as how to also utilise a chest CT to determine bone density, were also of interest. Furthermore, areas of application for emphysema quantification and opportunities for the automatic detection and quantification of arteriosclerotic plaques, were also examined,' Schoepf explains. The precision of pulmonary nodule detection achievable with this software is also currently being tested.



AI-based bone mineral density and vertebra measurements

Focus on the patient

Schoepf believes the value of AI application lies in its versatility: 'The applications are helpful because they deliver a comprehensive evaluation of functional imaging studies, providing us with a complete package of everything that may be important for the patient.' This is an important step towards patient-centred medicine because the focus shifts from the individual organs to the patient, their needs and the events occurring in different organ sections.

This interdisciplinary approach requires efficient communication between the medical specialists involved. Schoepf cites an example: 'If a radiologist is looking for plaques and then happens upon pulmonary nodules when the AI-Rad Companion Chest CT is used, they will pass on the result to the doctor in charge of treatment and may recommend further observation, a nuclear-medical examination or a biopsy.'

In the US, unlike in Germany, the patients are much more involved in their treatment. Even smaller hospitals offer increasing opportunities for all patients to have direct access to their medical records, so they can inform themselves about results and treatment plans. Schoepf believes this trend is positive: 'I think it's good that patients finally can take steps to maintain their health. It empowers them and I believe it's very important that patients become involved in their treatment plans and healing process.'

AI takes over quantifications

One large advantage of the use of AI in radiology is that it frees up valuable medical staff from laborious and time-consuming quantifications. The fear that AI will replace the radiologist has been sufficiently refuted, Schoepf underlines. 'This won't happen. The AI-Rad Companion is a very good example of how AI will help us to carry out work that nobody really likes doing, but which is easy for the computer.' Some examples for this are the quantification of coronary calcium and the quantification of emphysema (which is increasingly important due to advances in emphysema treatment) along with the next, logical step – measuring the aortic root for TAVI.

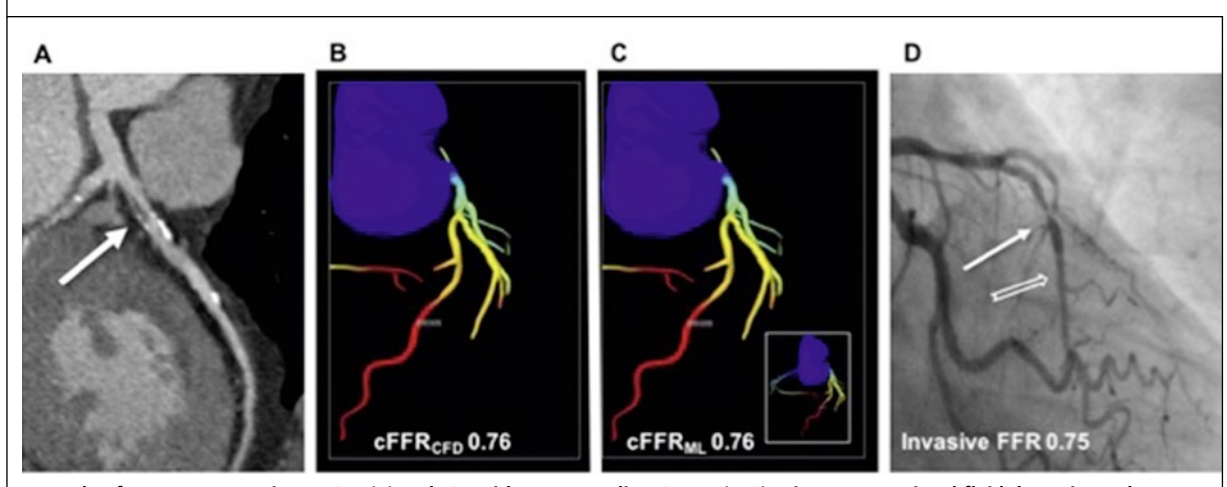
'The use of AI applications makes it ever easier to utilise all information contained in an X-ray or chest CT; this becomes obvious when we look at bone density measurements, which would usually require a separate, additional examination,' the professor enthuses. All results AI extracts from a chest image are automatically presented as a structured report so that the radiologist and referring doctor can draw conclusions for the treatment plan. This focused view into different organ areas also could be possibly used to comprehensively evaluate the effects of an individual hazard or individual cause of a disease – such as the constellation of calcified plaques, pulmonary nodules and pulmonary emphysema in smokers – in a lung cancer screening population, for instance.

The future – analyses based on deep learning

Schoepf believes that, in the future, the possible uses for AI in medicine will go way beyond the current capability of the Rad Companion. With the help of deep learning, computers could take over the independent evaluation of data sets to find correlations that, as yet, are unknown. 'This is one of the most exciting applications per se: the computer looks at everything with "fresh eyes" and tries to find correlations for which the human brain does not have the neural network capacity,' he explains.

There are already cases where a computer analyses a patient's entire medical record. If, in future, millions of data sets become available, computers will be able to use their evaluations to make new connections, such as those between factors that cause certain diseases, impact on life expectancy or bear specific risks. Deep learning, however, makes many – and not just lay people – a little uncomfortable because the users can no longer follow the individual steps of the computer's learning process. The expert is relaxed about this. 'This black box principle, i.e. the fact that we don't know why the computer makes connections, can lead to confusing results. However, ultimately, this means that we are challenged to scrutinise, examine or eliminate the results.' He forsees no risk of AI apps generating their own, dangerous momentum, neither in normal circ-umstances, nor in the distant future

Austrian-born **Uwe Joseph (Joe) Schoepf** is a professor with appointments in Radiology, Cardiovascular Medicine and Paediatrics at the Medical University of South Carolina (MUSC) in Charleston, SC. There he directs the Cardiovascular Imaging Division and is Director of Computed Tomography Research and a Director of the University Designated Centre for Biomedical Imaging. Schoepf grew up in Munich, Germany, where he graduated in medicine at Ludwig Maximilian University (LMU) and received specialist training at its Institute of Clinical Radiology. In 2001, already an accomplished radiologist, he left Munich to pursue his interest in cardiothoracic imaging at Brigham and Women's Hospital, Harvard Medical School, in Boston, MA. The professor joined MUSC in 2004.



Example of coronary stenosis on cCTA (A) and ICA with corresponding CT-FFR (B, C) using computational fluid dynamics and machine learning compared with invasive FFR measurement (D)

First BIOMONITOR III case in the Nordic region

Diagnosis in just three days


From left: Professor Jörg Carlsson, Dr Hendrik Schreyer and Dr David Olsson of the Department of Cardiology at Kalmar Hospital, Sweden, are the first physicians in the Nordic region to implant the device

It started as a fairly typical case: The 79-year-old patient had suffered unexplained dizziness for years. To diagnose why, the cardiology team at Sweden's Kalmar Hospital performed echocardiograms, Holter ECGs and other tests. However, these tests showed normal sinus rhythm and thus were inconclusive. Dr Hendrik Schreyer, Dr David Olsson and Professor Jörg Carlsson decided to use Biotronik's recently CE-approved Biomonitor III home monitoring system to finally identify the problem – becoming the first team in the Nordic region to inject the new implantable cardiac monitor (ICM). Three days later, during the daily data transmission, the monitor detected an arrhythmia and the hospital soon received the relevant clinical and technical information. The physicians then informed their patient that they had found atrial fibrillation and an asystole with an eight-second pause. Based on the diagnosis, they recommended pacemaker implantation.

'She was very pleased to get a call from us after only three days,' said Schreyer, who performed the injection. 'The device detected the problem very reliably. This is important because patients with ICMs often wait around four months until another episode occurs that gives us the information we need to make an accurate diagnosis.'

The Biomonitor III is designed to monitor a patient's heart rhythm long-term, transmitting data to the physician on a daily basis, to help them detect arrhythmia. Schreyer credits the system's signal quality for helping to simplify the diagnosis, noting r-wave amplitudes as high as 2 mV being registered on ECG readouts from the device.

Mild, moderate, severe, massive and torrential TI

Healing the heart's right chambers

Most people think their heart is located on the left side of their chest, and this is also the direction science has looked, so far. However, just as the heart sits at the centre of the chest, disease also affects the right side of the organ. Cardiologists must now look right to improve patient prognosis, according to Professor José Luis Zamorano, Vice President of the European Society of Cardiology, who will show at ESC 2019, how new classification can help patients suffering from disease affecting those neglected chambers located to the right side, Mélisande Rouger reports.

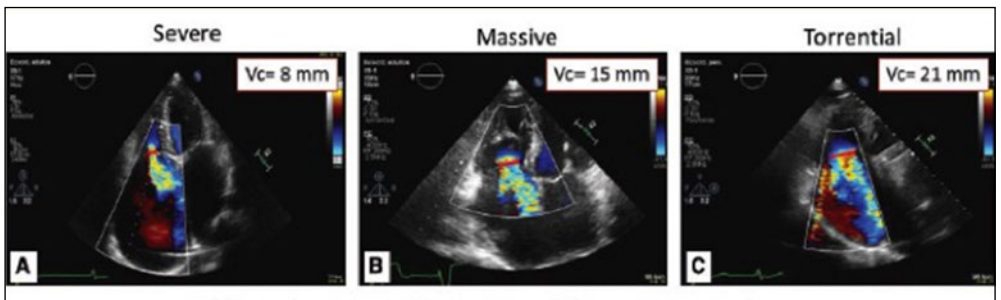
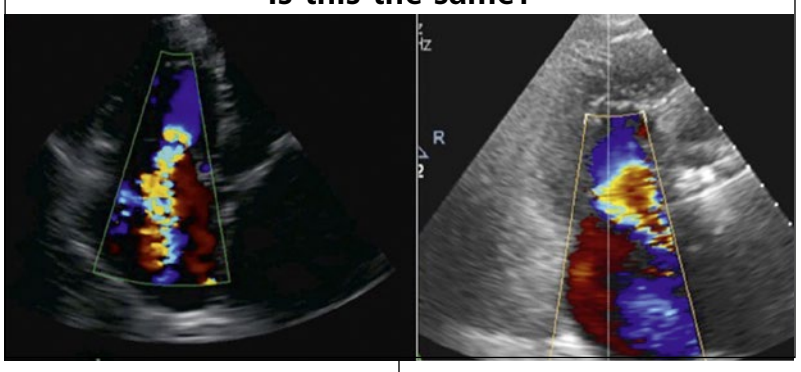


Table on the proposed expansion of the «severe» grade

Variable	Mild	Moderate	Severe	Massive	Torrential
VC (biplane)	<3 mm	3-6.9 mm	7-13 mm	14-20 mm	≥21 mm
EROA (PISA)	<20 mm²	20-39 mm²	40-59 mm²	60-79 mm²	≥80 mm²
3D VCA or quantitative EROA			75 – 94 mm²	95-114 mm²	≥115 mm²

Severe TR both cases
Is this the same?



The heart has four chambers: two ventricles – one to the left, one right and two atria – also located to the left and right. Most studies have focused on the aortic and mitral valves, both located to the left of the heart, and hence the most documented valvular diseases are those related to these chambers.

However, the tricuspid and pulmonary valves, on the right side, can also suffer illness. This means cardiologists need to be able to offer alternative therapies to those currently available, according to José Luis Zamorano.

In his presentation, Zamorano will discuss tricuspid insufficiency (TI) or tricuspid regurgitation, in which the tricuspid valve, which is located between the right atrium and right ventricle, does not close completely when the right ventricle contracts during systole.

'Tricuspid insufficiency is important because of its prognostic factor. The patient suffering significantly or severely from TI is at greater risk of death, or being hospitalized, or suffering heart attacks,' he explains. 'There's a higher mortality and higher morbidity.'

There is a new classification of TI and new mortality data. A couple of years ago, Zamorano and his research group at Ramón y Cajal Hospital, a leading institution in Madrid, published a new classification of this illness with five gradings – mild, moderate, severe, massive and torrential.

This year, in the European Journal of Cardiovascular Imaging, the Spanish researchers released a new study in which they found that patients with massive or torrential levels of tricuspid insufficiency had greater mortality rates than even those with severe levels.

'This is our newest finding: greater mortality rates are associated with severe and torrential tricuspid insufficiency,' Zamorano says, adding that this information will help practitioners to treat patients better.'

Once the medical team has prognostic implications and the means to classify disease, they can get to treatment. New devices are emerging that offer innovative ways of treating tricuspid regurgitation through percutaneous procedures, without the need for surgery or extracorporeal circulation. Six or seven such new tools have just been installed at Ramón y Cajal this summer, including Cardioband for the first time in Spain.

'With the prognosis that greater tricuspid insufficiency means greater mortality and so many new technologies with which to approach treatment, patients can now be treated better than ever,' Zamorano says.

Treatments are typically longstanding and based on diuretics, with medicines and pills. Some other patients, who are already going to be operated on for other valvular heart diseases of the left side, for example, the mitral valve, can have their problems with the right side fixed at the same time by the surgeon.

Patients who are at higher surgical risk can now benefit from these new percutaneous methods, without the need to open the patient's thorax or extracorporeal circulation.

Professor José Luis Zamorano is head of the cardiology department at Ramón y Cajal Hospital, Madrid, Spain, and Vice President of the European Society of Cardiology. He is Doctor Honoris Causa at Cuyo University, Argentina, and Professor of Medicine at Alcalá University in Madrid. He is also National President of the RDI for cardiovascular research at Carlos III Health Institute in Madrid.

New classification

Table 1

Proposed expansion of the 'Severe' grade

Variable	Mild	Moderate	Severe	Massive	Torrential
VC (biplane)	<3 mm	3-6.9 mm	7–13 mm	14–20 mm	≥21 mm
EROA (PISA)	<20 mm²	20–39 mm²	40–59 mm²	60–79 mm²	≥80 mm²
3D VCA or quantitative EROA[a]			75–94 mm²	95–114 mm²	≥115 mm²

VC, vena contracta; EROA, effective regurgitant orifice area; 3D VCA, three-dimensional vena contracta area.

[a] 3D VCA and quantitative Doppler EROA cut-offs may be larger than PISA EROA.

'So far, I haven't experienced another device with such a high signal quality. Most are under 1 [mV].' He also notes the cardiac monitor's clear p-wave visibility; a particularly important aspect for spotting atrial fibrillation.

The team finished the injection procedure in less than four minutes. Schreyer says the extra stability the device's tools afford helps to ease the procedure, because they allow an implanting physician to steady the main tool with his or her entire hand.

The ease of the injection procedure was quickly apparent to the patient as well. 'She was surprised, in the most positive way,' Schreyer noted, 'that she could go home immediately afterwards and had no complaints at all.'

New research indicates cardiac regeneration potential

Cells combination heals damaged hearts

Researchers have discovered a unique combination of cells grown from stem cells that could prove pivotal in helping a heart regenerate after a patient has suffered a myocardial infarction, Mark Nicholls reports.

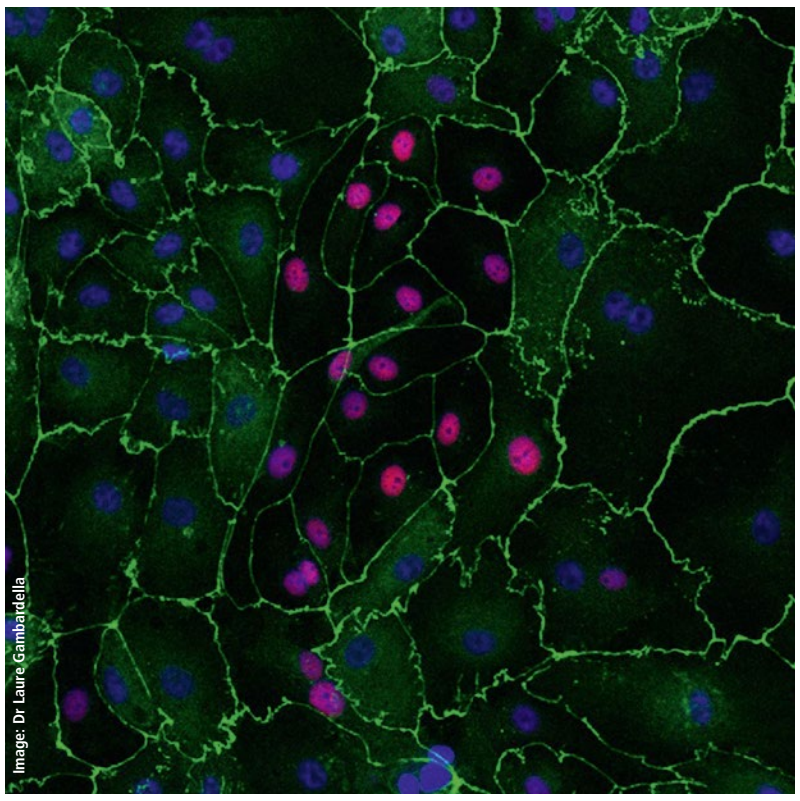
The University of Cambridge research team found that transplanting an area of damaged tissue with a combination of heart muscle cells and supportive cells, similar to those that cover the outside of the heart, might help the organ to recover from damage caused by a heart attack.

In Cambridge, consultant cardiologist Dr Sanjay Sinha and team – collaborating with researchers at the University of Washington, in Seattle – have used supportive epicardial cells developed from human embryonic stem cells to help transplanted heart cells to live longer. To test the combination, they used 3D human heart tissue grown in the lab from human stem cells and found that the supportive epicardial cells helped heart muscle cells to grow and mature and also improve the heart muscle cell's ability to contract and relax.

Transplanted cells restore lost heart muscle

In rat models, with hearts damaged through myocardial infarction, the combination also allowed the transplanted cells to survive and restore lost heart muscle and blood vessel cells. 'Basically what we have discovered is what we think is the right combination of cell types that will effectively regenerate a damaged heart. Dr Sinha, who is also a consultant cardiologist, said:

'People who have had a heart attack often do not have much viable muscle left, so the heart does not contract as well. What we would like to do is use stem cells to generate new heart muscle and then actually inject those new heart muscle cells into the heart.'



Epicardial cells, together with heart muscle cells, used in the study to regenerate the damaged heart. Both cell types are generated from human embryonic stem cells.

For the research, the team posed the question of how they could improve the function of cardiomyocytes from a stem cell that did not contract particularly well. Realising that epicardial cells are essential for cardiomyocyte to develop normally, the team mixed heart cells generated from a stem cell with epicardial cells. With the heart muscle cells and epicardial cells generated from embryonic stem cells, and the two derivatives injected to regenerate a damaged rat heart, the results are already proving significant.

'We found the grafts that regenerate muscle were two-and-a-half times as big in these animal models than if we did not have epicardial cells, so they make a huge difference to the amount of new muscle that is basically regenerating that damaged heart. I think that is a big step,' Sinha said.

'We found that epicardial cells were as good or better than any other cell type that we tried. The heart cells are more mature, they contract better, whole heart function is better and there are more blood vessels inside new heart muscle.

'Heart cells do not work best by themselves. They need other cell types to support them. We know these epicardial cells are great supporting cells when the heart develops, so we are using that same principle to support the heart cells when we regenerate the heart.

'The beauty of this approach is that nature has been telling us the answers all along because, in development, this is what nature does, it gets different cell types to work together. We have just taken that principle from development and applied it now to regeneration.'

More success than other centres

Sinha hopes his team's approach will be more successful than that of other centres that have generally focused only on heart muscle cells. 'We have shown that a combination of cell types works much better than heart muscle on its own,' he confirmed, although he acknowledged there is some way to go before using the cells in human patients.

From trials in rats, the team plan to validate their findings in a larger system, such as a pig model, with a view to first-in-man trials in five years' time.

He is confident the current discovery is a major step forward and praised Dr Johannes Bargehr, first author of the study, and the Cambridge team, as well as Professor Chuck Murray in Seattle, USA. 'We should also acknowledge the patients who have damaged hearts and heart failure,' Sinha added thoughtfully. 'I see them in hospital and they are the inspiration for what we do.'

Transplant is the main treatment for heart failure, so finding an alternative is essential.

BHF Medical Director Professor Sir Nilesh Samani said: 'When it comes to mending broken hearts, stem cells haven't yet really lived up to their early promise. We hope that this latest research represents the turning of the tide in the use of these remarkable cells.'

Dr Sanjay Sinha is a Senior Research Fellow at the University of Cambridge (funded by the British Heart Foundation) and an Honorary Consultant Cardiologist at Addenbrooke's Hospital, Cambridge. His research interests focus on the use of stem cells to understand and treat heart disease.

Beating tissue regenerates cardiac muscle

Patching up a damaged heart

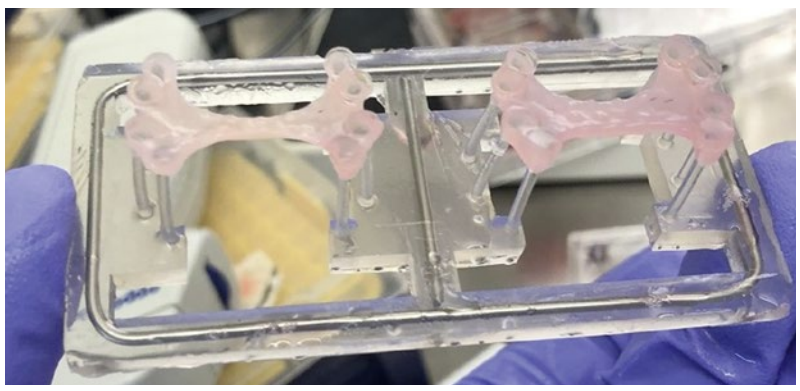
Report: Mark Nicholls

Scientists in the UK have developed tiny patches of engineered heart tissue that have the potential to be implanted to help people recover from a heart attack.

Measuring approximately 3cm x 2cm, the patches contain up to 50 million human-induced pluripotent stem cell derived cardiomyocytes (hiPSC-CM). Yet, these are programmed to turn into working heart muscle that can beat and gradually be incorporated into damaged muscle to help reverse any loss of pumping ability sustained due to myocardial infarction (MI).

Richard Jabbour, Tom Owen and the research team from Imperial College London are now keen to design clinical trials to test the safety of the patches and see whether they are equally effective in humans.

The rabbit experiments revealed heart function improvements after MI and after four weeks the left ventricle (which pumps blood out through the aorta) was recovering without developing any abnormal heart rhythms.



Stem cell patches rotated

Most significantly, the lab-grown patches appeared to be nourished by blood vessels growing into them from the recipient heart.

The research has been led by Sian Harding, Professor of Cardiac Pharmacology at the National Heart and Lung Institute, Imperial College London (ICL), and Director of the BHF Centre for Regenerative Medicine, who explained that her team has worked on the beating heart patches since 2013 to create new cardiac muscle and target loss following a heart attack.

Their work was inspired after the approach of injecting stem cells directly into the myocardium in research at other centres showed limited success with the heart ejecting the cells and triggering arrhythmias. While injection of large numbers of cells disrupted the delicate construction of the heart and produced arrhythmia, Professor Harding said the new beating patches – which have a spontaneous rhythm – have offered more promising results as they are sutured lightly on to the heart surface and then covered by the pericardium and they begin to establish a connection to the heart.

'We do not know very clearly yet whether they have any electrical coupling, certainly not at an early stage, but there is a possibility that there is a mechano-effect: with the patches on, the heart stretches and relaxes; it could automatically synchronise the patch with it.'

The team also noticed that the patches did not produce arrhythmias as in the rabbit model, unlike what happened when large amounts of cells are injected into the centre of the myocardium.

Up to 60 million cells are being produced a week in the ICL lab that are 95-98% pure cardiomyocytes and 'trained' to develop stronger contractions in unison with the cells placed in hydrogel, which induces the cells to establish connections. 'When they are placed together in the hydrogel they start to beat and join up,' she said. 'They're suspended between flexible silicone posts so that when they do beat they pull the posts together and because they are doing that, they are exercising against a load so they develop a much stronger contraction.'

The patches are designed to beat spontaneously after three days and mimic mature heart tissue within a month. They also release natural chemicals that would stimulate the heart cells to repair and recover.

'We had thought about a patch bigger than 2cm x 3cm, but surgeons advised us that these were suitable, and that a larger number, perhaps 10-15 of them, could be used and then deployed in areas where they saw most damage.'

The research is carried out at the London BHF Centre of Regenerative Medicine where Imperial College London research teams, along with partner universities in the UL and Hamburg focus on innovative ways to get the heart to regenerate.

With a view to first-in-man trials in 2-4 years, the next step is in ensuring the cells are GMP (Good Manufacturing Practice) compliant and conducting a further pre-clinical trial in the rabbit model.

£11,000 per treatment

By using more than one patch, the team is confident the therapy can match the one billion cells lost during a heart attack and will also be cost effective at about £11,000 (12,300 euro) per treatment.

'We hope the cells will integrate or add to the contractility of the heart,' Harding added. 'We have

Ready to be aired at ESC 2019

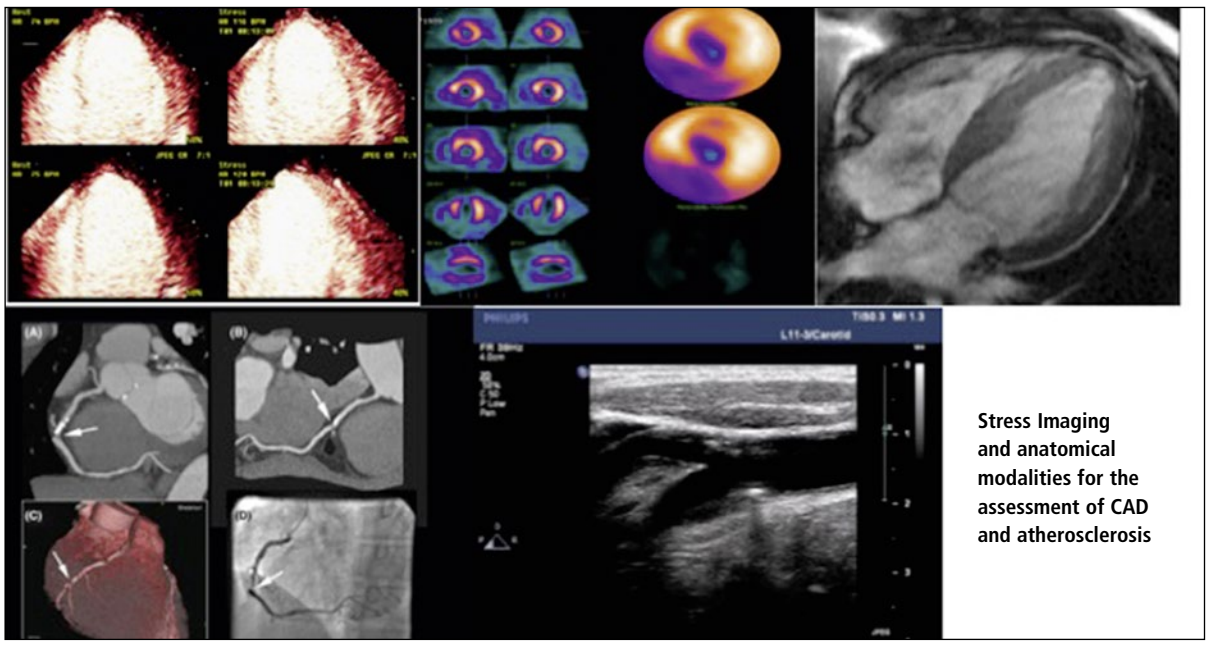
Imaging controversies in coronary artery disease

ESC Congress, Paris: Two key strands in the 'Controversies in imaging coronary artery disease' session at the congress will examine the pros and cons of imaging use for coronary artery disease risk stratification in asymptomatic patients; the second strand will focus on whether CT angiography should be the first choice for imaging coronary artery disease in patients with stable chest pain.

Co-chair Roxy Senior, Professor of Clinical Cardiology at the National Heart and Lung Institute, Imperial College London and Consultant Cardiologist and Director of Echocardiography at the Royal Brompton Hospital, London, explained that different viewpoints remain within this field.

'The jury is still out regarding added value of imaging beyond cardiovascular risk factor modification in asymptomatic individuals,' he explained. 'This is largely because there are no adequately powered, randomised studies demonstrating the added value of imaging beyond risk factor modification that has been shown to improve outcome in such patients.

'These studies are perhaps not yet done because of the large number of patients that need to be recruited to show a difference in outcome because of low event rates in these asymptomatic patients.



Stress Imaging and anatomical modalities for the assessment of CAD and atherosclerosis

Stress imaging

'The controversy of the second topic stems from the fact that CT angio views the coronary arteries but does not provide the functional significance in terms of causing ischaemia of moderate grade lesions versus other forms of cardiac imaging, namely stress imaging, which establishes myocardial ischaemia as the cause of the chest pain.'

Senior added that, in patients with suspected angina, the major question is whether the chest pain is due to myocardial ischaemia. He said stress imaging answers this question, but CT does not, unless it shows severe lesions.

'On the other hand,' he continued, 'CT angio can rule out coronary artery disease as the cause of chest pain and, at the same time, identify milder forms of CAD for which preventative measures may be instituted.'

He also said the absence of myocardial ischaemia does not rule out the presence of CAD albeit not severe enough to cause ischemia. 'However, it is yet to be conclusively established that identifying such lesions and instituting preventive lesions can improve clinical outcomes.

The functional significance of coronary stenosis

Lately, it has also been shown that CT angio can also assess the functional significance of coronary stenosis, however, its clinical efficacy is yet to be demonstrated in a real-life scenario.'

Recent ESC/AHA/ACC guidelines say that stress imaging, including Exercise ECG, (only in low risk patients with normal baseline ECG) is the first line test in patients with stable chest pain. Carotid ultrasound for atherosclerosis and CT of coronaries for assessing calcium load are recommended in intermediate risk asymptomatic subjects, though they clearly state that this remains controversial.

'The important fact to consider is, over the years, mortality in patients with suspected stable angina has reduced considerably and in fact a positive test, such as myocardial ischaemia and incidence of flow-limiting CAD on CT is down to around 10%,' Senior added.

Needed? An adequately powered randomised study

'Hence tests that are low risk/low cost but at the same time accurate should be employed – for example, ultrasound-based tests such as stress echo combined with carotid ultrasound for the assessment of atherosclerosis may be employed.'However, Senior also states that an adequately powered randomised study vs CT angio may still need to be performed.

The ESC session will explore a number of these key questions through expert presenters – topics, Senior said, that are clinically very relevant and highlight a dilemma regularly faced by cardiologists. 'We have excellent speakers with great experience in this field,' he added. 'I am hoping the delegates at the end of the session will have an excellent knowledge of the literature and can make informed decisions in their clinical practices despite the controversy.'

* 'Controversies in imaging coronary artery disease'.
The Hub, ESC 2019 Paris.
2 September 2019. 4.40-5.50pm.

Roxy Senior is Professor of Clinical Cardiology at the National Heart and Lung Institute, Imperial College London and Consultant Cardiologist and Director of Echocardiography at the Royal Brompton Hospital in London. He is also the Director of Cardiac research at the Northwick Park Hospital, Harrow. He obtained his Masters' degree in medicine and cardiology from the University of Calcutta, India, and came to the UK in 1989. He became a Consultant Cardiologist and Director of Cardiac Research at the Northwick Park Hospital in 1995 and took up his current role in 2010. With a major interest in echocardiography – and particularly in heart failure, coronary artery disease, valvular heart disease and acute coronary syndrome – the clinician is recognised as a pioneer of the clinical development of myocardial contrast echocardiography.

Sian Harding is Professor of Cardiac Pharmacology at the National Heart and Lung Institute, Imperial College London, and Director of the BHF Centre for Regenerative Medicine. A primary focus of her work is on cardiomyocyte function in the failing heart, and gene therapy to modulate cardiomyocyte function, also, more recently, on the characterisation of cardiomyocytes derived from embryonic stem cells, and their use in cardiac repair, tissue engineering and drug discovery. The professor is also Past-President of the European Section at the International Society for Heart Research and Fellow of the AHA, ESC and ISHR.

seen they significantly improve rabbit heart function after myocardial infarction.'

Along with help helping to regenerate heart muscle damage, the team believe they will benefit, patients who have established scarring after an MI, rather than straight after MI or revascularisation.

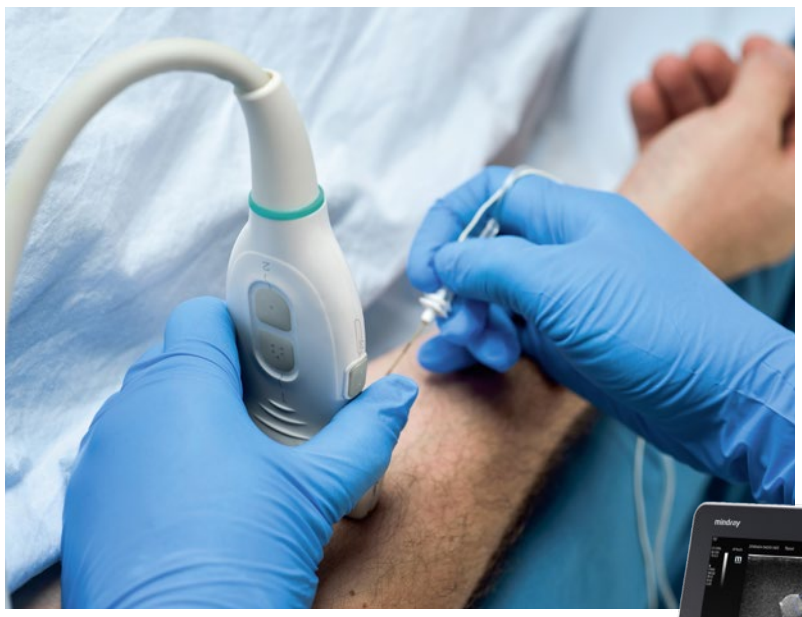
POC ultrasound shines in intensive care

Pre-set assets and 4-D needle navigation

Professor Felice Eugenio Agrò is Director and Chairman of the Postgraduate School in Anaesthesia and Intensive Care at the University Campus Bio-Medico of Rome. During our recent interview he spoke of the need for safe and accurate methods in ICU procedures. Many strong factors in this are related to ultrasound use in everyday clinical practice, he stressed, adding that these include portability, ergonomics and user-friendliness. 'Obviously, a portable unit with advanced ergonomics becomes very crucial to be effective and precise. That's why tablet solutions are becoming even more appreciated, since ergonomics is becoming key.'

Equipment chosen for use at his ICU includes, for example, Mindray's TE7 ultrasound system. 'In our experience TE7 offers very safe, accurate and convenient solutions in anaesthesia – not only because we can obtain great imaging in soft tissue and identifying structures, but we also have a real-time feedback and good visualisation of the needles in the imaging plane,' he explained.

'The TE7 touch screen system provides very good image quality, which is crucial to make rapid patient care decisions. In the era of smartphones and tablets, intuitive gesture controls provide an important help in being fast and effective. I believe that efficient focused point-of-care exams would minimise the user learning curve, with no need to navigate a knob keyboard, as in many laptop-like and cart-based ultrasound solutions.'



'This solution seems to be very promising and the initial outcome is very safe, fast and accurate, increasing efficacy and patient comfort,' Agrò observed.

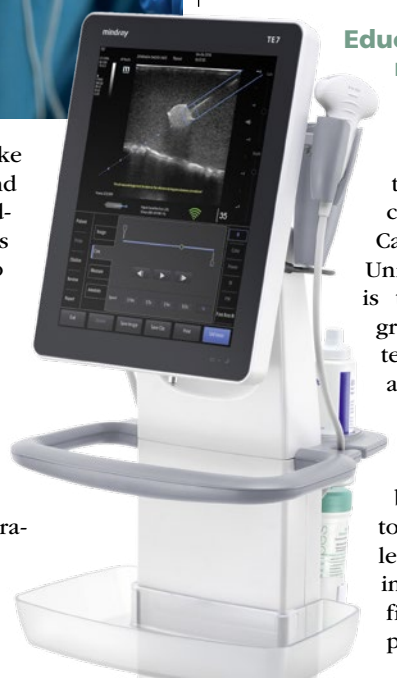
Locating a needle tip in freehand technique

'In general, ultrasound is not good for locating a needle tip, either out of plane or in plane, in freehand technique, since it becomes difficult to align the needle with ultrasound plane and plan trajectory pre-puncture,' he explained. On the other hand, using a biopsy kit the needle-guided bracket is not flexible. All these issues make standard ultrasound needle access guidance techniques quite difficult to learn.

'Based on magnetic field induction technology, real-time position detection and orientation of the needle, displayed on the ultrasound image, enhance ultrasound guidance. This way it's possible to predict the trajectory and best scanning approach to reach the target before inserting the needle into the region of interest. With this innovative approach we believe that the learning curve of doctors, which is approaching free-hand access, will decrease with the result of very accurate and confident needle accesses.'

'It's important to have systems suitable for a disinfected and sterile environment with the possibility of easy cleaning and sterilisation,' Agrò added. 'We are talking about a medical environment where we deal with needles, in which safety and effectiveness should be going in the same direction.

'We appreciate that we can use the TE7 using gloves, no matter that it's a touch-screen tablet unit. Also, the screen is non-porous, which can easy be disinfected without turning off the unit, thanks to a locking feature.'



Education and research

The objective of the Postgraduate School of Anaesthesia & Intensive care at the Campus Bio-Medico University of Rome is to pro-mote integrated structures of teach-ing, research and healthcare, Agrò said 'We plan to provide students with the best technology to speed up their learning curve and increase their confidence for a better patient throughput.'

Felice Eugenio Agrò is Professor of Anaesthesia and Intensive Care, Chairman of the Postgraduate School of Anaesthesia and Intensive Care and Director of the Department of Anaesthesiology, Intensive Care and Pain Management at the University School of Medicine Campus Bio-Medico of Rome, Italy. He has also been the Medical Director and Director of Health Strategy & Business Development for about a decade. He has authored and edited numerous medical publications and reviews manuscripts in Critical Care Medicine, Anaesthesiology, and for the Journal of Clinical Anaesthesia, European Journal of Anaesthesia, British Journal of Anaesthesia, Minerva Anestesiologica etcetera. His research focus lies on airway management, mechanical ventilation in anaesthesia and intensive care, pain management, body fluid management, the evolution of neuromuscular monitoring, haemodynamic monitoring: invasive and non-invasive clinical application. He has been among the Book of Experts for the Ministry of Education, University and Research since 2002. In 2008, he received the Commander to the Order of Merit of the Italian Republic medal from the President of the Italian Republic.

Ultrasound can assess intracranial pressure in emergency

A future gold standard tool

Report: Mark Nicholls

Whilst researchers acknowledge ultrasound, when used as a tool to assess intracranial pressure in an emergency, is not a replacement for current gold standard invasive approaches, they believe it has enormous potential as a non-invasive and fast, cost-effective, and patient-friendly way to assess possible brain injury at a patient's bedside.

Consultant anaesthetist Dr Chiara Robba, a specialist in the field, suggests the use of ultrasound for intracranial pressure (ICP) assessment can become standard practice in the not too distant future.

In recent years, Robba, from the San Martino Hospital in Genoa, has worked with colleagues at the University of Cambridge, United Kingdom, to explore the suitability of ultrasound to conduct brain scans in an emergency setting.

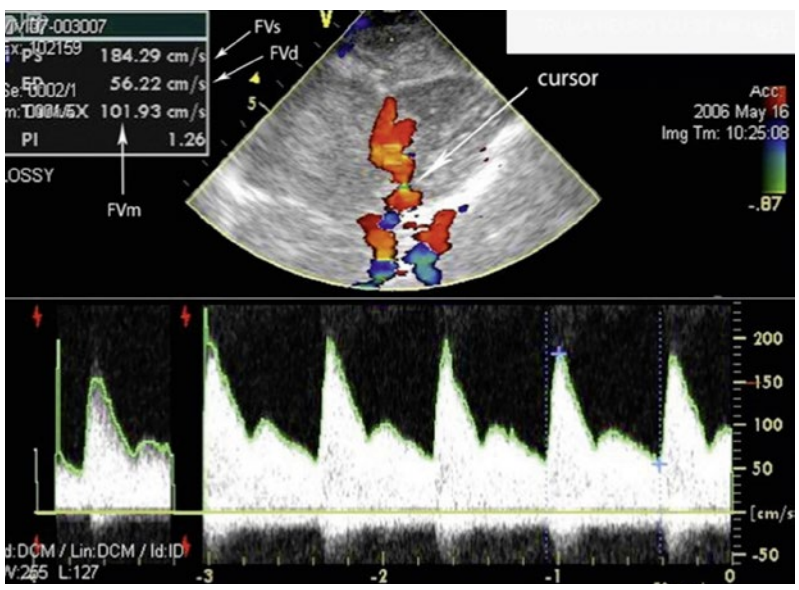
One recent study compared the relationship between ultrasound-based non-invasive ICP (nICP) and invasive ICP measurement in neurocritical care patients and found that it was a 'promising and easily available technique for identifying critically ill patients with intracranial hypertension'.

She outlined latest developments in the field during her presentation 'An update on the use of US for the estimation of intracranial pressure in emergency' at the 21-24 February annual congress of WINFOCUS (World Interactive Network Focused on Critical Ultrasound), held in Dubai.

'Over the last few years, we've realised that the use of ultrasound for the brain is suitable in an emergency setting,' Robba explained. 'When a patient arrives in the emergency department, a doctor performs an assessment of the body using ultrasound and that generally includes assessment of the heart, lungs and abdomen, but not the brain.

A wide range of pathology

'But you can use ultrasound to provide a lot of information, even when the patient has just arrived in the emergency department. That includes a wide range of pathology like increases of intracranial pressure or reduction of cerebral perfusion pressure or you can also have a direct assessment and visualisation of intracranial haematoma or haemorrhage.'



Non-invasive ICP can be estimated through waveform analysis of the main cerebral arteries. This is an example of transcranial colour duplex sonography with the insinuation of the middle cerebral artery.

A key reason why ultrasound has not been used previously in this context is due to difficulties of accessing the brain encased in the skull. 'Ultrasound waves cannot pass through the bone so sometimes it's difficult to visualise the brain,' Robba pointed out. 'But if you use the "windows" – temporal, transorbital, submandibular and suboccipital windows – you can have a proper look at the brain.' This is also a valid care sandard for patients who undergo decompressive craniectomy, she added.

Use of ultrasound for ICP assessment requires training, commitment and study, but Robba believes this should be encouraged because of the benefits. 'You can visualise cerebral pathology; get early identification of intracerebral haemorrhage or intracranial cerebral complications without having to transfer the patient for a CT scan, which can be painful for a patient who is haemodynamically unstable. Also, CT requires the use of radiation and cannot be performed at a patient's bedside, so the advantages are many.'

Her study team in Genoa and Cambridge is setting up training programmes and writing a book to complement courses already available at Cambridge University.

While there remains a lack of awareness of the potential of this relatively new technique, she believes it can become a care standard for patients in emergency units, intensive care or the operating theatre where patients are at risk of neurological complication, as well as at the bedside and to be used in the same way ultrasound is deployed to monitor the rest of the body.

For a clinician, she explained, performing a brain ultrasound at the bedside can identify issues of concern and prompt further tests – or offer reassurance that all is well. 'From a patient's perspective, it is safe monitoring, does not cause any harm but adds information. When it becomes routine clinical practice, it's going to reduce the number of CT scans, the number of radiation exposures and transfers.'

20 international experts

Over the last two years, exponents of the technique – including Robba – have been presenting US potential at conferences, and she is currently working with 20 experts from around the world on a consensus paper as well as looking at training requirements, standards and competences for practitioners to be able to use ultrasound as a technique to assess the brain, including the estimation of ICP in an emergency.

Yet, amid the enthusiasm for the

Injured mountaineers gain in-depth exams

Ultrasound climbs the heights

Dr Philippe Mahiou practices anaesthesia in the Grenoble area, splitting his time between a private clinic and working as a helicopter doctor to attend mountaineering accidents. As part of his work, Mahiou routinely uses ultrasound, and understands the importance of the technology to guide anaesthesia in the operating room and assess patients in the field.

Dr Philippe Mahiou uses ultrasound to visualise very small nerves in the feet.

When anaesthetist Dr Philippe Mahiou described his use of ultrasound, he explained: 'Around 80 per cent of my work is at the Clinic des Cèdres, a private clinic near Grenoble, where approximately 7,000 to 8,000 trauma and orthopaedic procedures are performed every year. I frequently use ultrasound to guide injections for locoregional anaesthesia, after first discovering the benefits of this technique in 2007. The main advantage is that you can visualise the nerve very precisely; it's not necessary to use neurostimulation to look for the nerves instead.

'Our Fujifilm SonoSite systems offer excellent image quality; you can even visualise nerves in the feet, which are very small and often hard to see. It is also easy to move the systems around and adjust their height, which is perfect for point-of-care applications. Additionally, we can save images and export them, which is great for teaching, as are the locoregional anaesthesia educational training videos on our X-Porte systems.'

Alpine ultrasound exams

'The remaining 20 per cent of my work is as a mountain rescue doctor for the Grenoble University Hospital. I've been in this role for 18 years or so. After using ultrasound for anaesthesia in the operating theatre, I began using it on mountain rescues over 10 years ago. People who have mountaineering accidents often suffer from all kinds of thoracic, cerebral, abdominal, spinal and pelvic injuries, and so it's vital for us to reach and treat the patient as quickly as possible. For this reason, the mountain rescue heliport is based in Alpes d'Huez, which reduces the average intervention time.

'We're the second largest mountain rescue base in France after Chamonix, and receive about 1,000 calls per year from the Grenoble Operations Centre, which gives us the coordinates we need to reach each patient.

The team is made up of five individuals; a pilot, mechanic, two rescuers, a doctor, such as myself, and in avalanche cases we often also use rescue dogs. We carry the same kit as an emergency department – all the equipment necessary to resuscitate in the field – packed into two bags. The first bag weighs about 25 kg, and carries all of the equipment to reduce and try to stop heavy bleeding, or treat patients suffering cardiac arrest, as well as our portable ultrasound system, while the second bag contains supplementary equipment for resuscitation.'

Triage and monitoring

'We use ultrasound as part of the clinical examination of each patient to diagnose any problems, assist with pain management and monitor them on route to hospital. We therefore need a compact and robust device that can start quickly and be used in extreme conditions. When we arrive at a patient, we start by checking the pulse, blood pressure and respiratory rate, before performing an ultrasound scan. We begin with a FAST examination – to check whether there are any transabdominal effusions – then we use ultrasound to guide regional anaesthesia for pain management, including femoral, interscalene, infraclavicular, medial, radial and ulnar blocks as required.

'We often also conduct pulmonary, cardiac and transcranial Doppler ultrasounds to help us decide which hospital is best to send the patient to, depending on the severity of the trauma. A lot of our patients suffer cranial injuries, and identifying these means we can send patients straight to the neurosurgery department on arrival at the hospital, for more immediate emergency treatment. Another benefit of ultrasound is that you can use it to monitor a patient if their health is deteriorating. For instance, we regularly repeat FAST examinations and discover transabdominal effusions that hadn't had time to form before we conducted the initial scan.

Overall, ultrasound is a really valuable and versatile tool both in the clinic and out in the field. It has improved the quality of patient care immensely. I don't know what I'd do without it.'

Chiara Robba is a consultant in anaesthesia and intensive care at the San Martino Hospital in Genoa and an honorary consultant at Cambridge University Hospital in the UK. Her research interests cover ultrasound for intracranial pressure, traumatic brain injury, intracranial haemorrhage, and areas of general intensive care, including mechanical ventilation and sepsis.

new development, Robba also urges caution because the scientific evidence still needs to be assembled and she stressed the technique should not replace the gold standard invasive methods to measure brain trauma pressure because there are limitations to the ultrasound approach with just the four "windows" for assessment.

However, Chiara Robba concluded: 'The benefits are potentially huge. In the future I think this should become a standard of care in the same way as echocardiography is for the heart.'

UK tests high-speed remote medical diagnosis

Ultrasound scanning via a 5G network

Report: Mark Nicholls

To demonstrate advances in 5G connectivity for healthcare, a UK team has linked a paramedic in a simulated ambulance to a hospital-based clinician.

The paramedic wore a robotic or 'haptic' glove, which received signals over the live 5G network. Using a joystick, the clinician remotely directed the paramedic to move the ultrasound sensor to where on the patient the clinician wanted to scan.

From left: Gerry McQuade, CEO of BT Enterprise, with Fotis Karonis, BT 5G Executive Advisor, and Cameron McVittie, Operations Manager at West Midlands Ambulance Service, with the haptic glove and ultrasound used in the ambulance simulation

Really high quality and in real-time

From this examination, high-quality ultrasound images were transmitted to the clinician in real-time, over the high-bandwidth 5G connection. In addition, a camera in the ambulance transmitted images of the paramedic and the patient to a second screen at the clinician's workstation to offer an overall view.

Andy Street, Mayor of the West Midlands, tries out the haptic glove alongside Omkar Chana, from WM5G, and Fotis Karonis and Jeremy Spencer from BT, watched by Paramedic Cameron McVittie, Operations Manager at West Midlands Ambulance Service

WM5G – which aims to accelerate deployment of the infrastructure needed for 5G, and is building health, industry and mobility testbeds in the West Midlands region – pointed out the benefit of enabling ultrasound scans to be performed in the field, and reviewed remotely, facilitates quicker diagnosis and onward treatment.

The demonstration was hosted by the Medical Devices Testing and the Evaluation Centre (MD-TEC), in the University Hospital Birmingham (UHB) simulation lab, at the Institute of Translational Medicine, along with British Telecom (BT), the West Midlands Ambulance Service, and WM5G. '5G will help us to roll out this next generation of healthcare technologies,' said Tim Jones, UHB Chief Innovation Officer. 'In the future, our clinicians will be able to deliver holistic specialist advice in real time, potentially forming virtual multi-disciplinary teams to provide the best patient care using intelligent IT links.'

Dr Omkar Chana is programme director for citizen wellbeing at WM5G, covering health and social care and the emergency services. With a PhD in physics, his career has covered hi-tech data and analytics and business strategy specific to the NHS and healthcare, as well as mergers and acquisition.

Doing what you cannot do with 3G or 4G

Dr Omkar Chana, WM5G programme director, added: 'The ultrasound demonstration was a flavour of what we can really do with 5G. You cannot do that with 3G or 4G. And, although it was 5G ultrasound, what we are demonstrating can lend itself to any aspect of clinical imaging and real time communication. Also, it does not have to be in an ambulance, it can be in a care home, or GP surgery, and the image quality is just as good as it would be in a hospital.'

Tim Jones is Executive Chief Innovation Officer at University Hospital Birmingham. He joined UHB in 1995, became Head of Service Improvement in 2002 and led the New Hospital Clinical Redesign Programme, before being appointed to the role of Chief Operating Officer in June 2006. In September 2008, he was appointed Executive Director of Delivery, which incorporates board level responsibility for Research & Innovation, Education and Workforce.

The NHS long-term plan

Technological solutions – driven by 5G - are at the forefront of the latest NHS Long Term Plan as the NHS endeavours to meet the challenges of increased demand and an ageing population. 'With low latency and the ability to communicate in real time, coupled with faster speed, massive amounts of data can be put through. With ultrasound, the clinician can see everything in real time. If he says "move left", the paramedic in the ambulance moves the probe left – immediately,' Chana observed. 'It means the clinician can decide that the patient may not actually need to go to hospital, or may need to be taken to hospital quickly and go straight into surgery because of what they see on scan.'

Education and

Assessing the AI revolu

How will artificial intelligence (AI) affect continuing education and management in radiology? This issue was discussed by an expert panel at the ESR AI Premium meeting in Barcelona, Mélisande Rouger reports.

Professor of radiology and director of the Academic Department of Radiology and Medical Informatics at the University of Geneva, Switzerland, **Christoph D Becker** also chairs the radiology department at the University Hospital. Formerly a radiologist at the University Hospital of Berne, and accredited as Privat-Docent at Berne University, in 1994 he became an abdominal and interventional radiologist at the university hospital in Geneva, and later was professor and vice-director of the radiology division, and since 2004, its director. He also chairs the Academic Department of Radiology and Medical Informatics. Since 2018, he has participated in the creation of the new Diagnostic Department at the hospital with the long- term objective of combining the information of medical imaging, pathology, and genetics in an integrated report

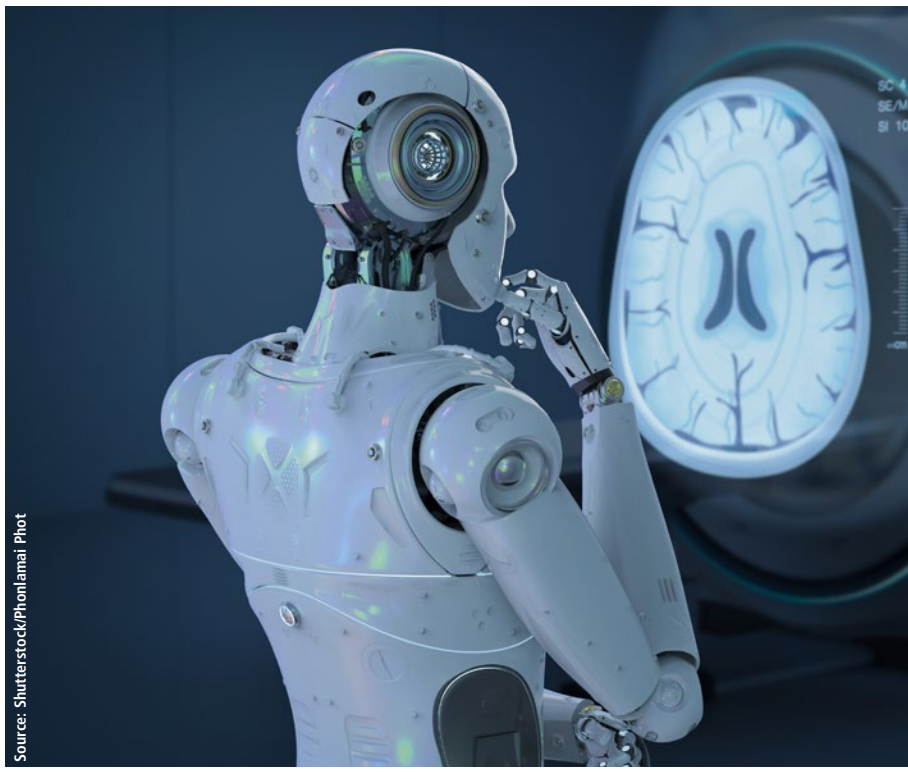
Continuing education – It must be clear what radiologists need to learn about AI; one way to go could be to give it more space in the training curriculum, according to Elmar Kotter, deputy director of the radiology medical centre at Freiburg University. 'We need to integrate imaging IT, and especially AI, more into the curriculum than it is today, through dedicated AI and informatics modules.'

AI should be treated like a new modality to be properly used in daily routine. 'This requires continuous learning for everyone. We have to define what is the minimum AI learning, so that everybody knows the basics. For those who want deeper knowledge and certification, the ESR and European Society of Medical Imaging Informatics are preparing a diploma,' explained vice president of the society Kotter.

It should also be clear what AI can and cannot do in a given institution, and how algorithms are validated, a task only radiologists can do. 'We must understand how AI is integrated into our workflow and how our interaction with AI is working and can be optimised. Knowledge of medical legal aspects and ethical implications is also mandatory,' he added.

Online resources to help are increasing. Micro learning, with content from scientific societies and radiology editors is a trend, along with dedicated apps and social media. Systems that pre-process and make data analysis to access random information are emerging. For example, so-called cognitive radiology assistants present the radiologist with the right images, ask the referring clinician relevant questions and allow for efficient answers for radiologists, by providing possible relevant data for image interpretation.

'Such systems give comparative cases already in your PACS system and could also give access to the relevant part of patient history in this case,' he explained.



Source: Shutterstock/Phonlamai Phot

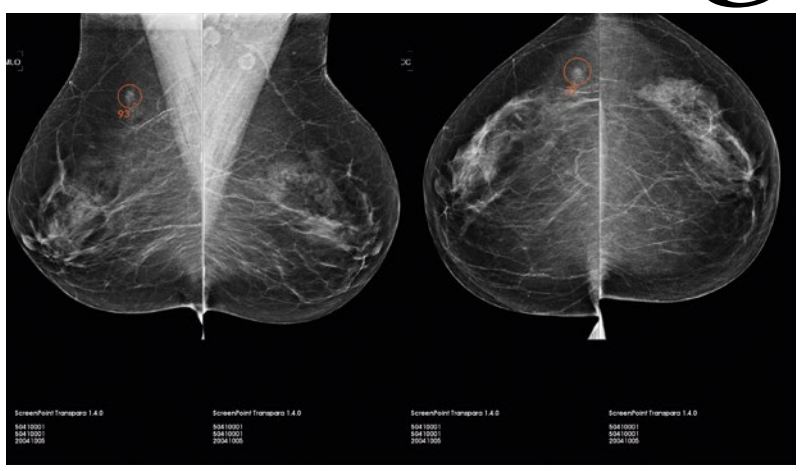
Solutions that offer access to both archive and information should allow faster learning curves for radiologists, by providing similar cases

Artificial intelligene technology continuously evolves

AI value in breast screening

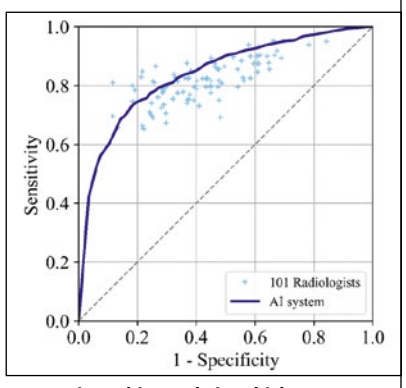
Although breast cancer (BC) mammography screening enables early detection of breast cancer, mammography presents issues such as variability between the radiology readings and shortage of radiologists. This area of medical imaging is where artificial intelligence (AI) could help make the biggest difference and improve patient outcome, a Netherlands-based researcher told delegates at an April meeting in Spain.

Report: Mélisande Rouger



Transpara, the AI software for 2-D and 3-D mammography, developed at ScreenPoint. The 2-D version has received CE and FDA approval.

Millions of mammograms need to be read annually, putting a strain on radiology services. Computer aided diagnosis (CAD) emerged more than 20 years ago for second readings, with markers that highlighted the area of evaluation for further inspection. Overall, the benefit of using CAD is disappointing, Albert Gubern-Merida, an AI researcher in Nijmegen, explained at the ESR AI Premium meeting. 'These systems all target the perception level and just help the radiologist double check things that could have been missed. Besides, those algorithms are outdated,' he pointed out.



Peer-reviewed journals in which Transpara was independently validated, both used standalone or combined with radiologists.

AI systems today are trained on millions of images and associated data. 'Mammography is the best area of application because thousands of mammograms are generated daily around the world and need to be read,' said Gubern-Merida, Head of Research and Development at ScreenPoint, a company with commercially available AI software for 2D and 3D mammography.

Performance of some current AI systems is at least equal to human performance, research published in the Journal of National Cancer Institute suggests. At Radboud University Medical Centre, researchers independently tested Transpara software vs. 101 radiologists, collecting both multiple centre and multivendor data sets. They showed that the algorithm was performing as well as the radiologists' [Stand-Alone Artificial Intelligence for Breast Cancer Detection in Mammography: Comparison With 101 Radiologists. JNCI: Journal of the National Cancer Institute, 2019 djy222.]

Machines will not replace radiologists

Equal performance does not mean machines will eventually replace radiologists. 'It's not going to happen, but we need to use this clinically proven, high quality technology to improve the care we give to women,' Gubern-Merida emphasised.

There are various ways to apply these technologies, which can improve clinical performance workflow, especially in detection and decision support, recent research suggests [Detection of breast cancer using mammography: Impact of an Artificial Intelligence support system. Radiology. 2019 290:2, 305-314.]. 'AI tools can highlight things that shouldn't be missed without interrupting the reader; or, AI results can simply be requested when a second opinion is needed. Studies show that radiologists improve both specificity and sensitivity using these algorithms,' he said.

AI may positively impact on workflow by reducing radiologists' workload. BC mammography screening means reading many images. Second reading improves detection, but this approach might be unsustainable with the introduction of Digital Breast Tomosynthesis, since the reading time increases twofold compared to 2-D mammography. Having an AI system that immediately helps to differentiate exams with and without suspicious lesions could help save a lot of time and trouble.

'AI systems can produce a score, to detect and determine the risk of cancer presence in an exam. Usually there's a score from 1-10 or 1-100,' he explained.

One simple application, possible today, is through the work list, by sorting and labelling exams by their risk of having a cancer – for instance, from the most likely cases to more likely ones, less likely ones, etc. and dividing tasks based on a radiologist's schedule.

AI should make decisions

With an ever-thinning radiology workforce, he suggested, 'Let AI decide if a second radiologist is needed to read a scan. AI systems are exceptionally good at reading normal scans, so let AI do that.'

Questions from users and ongoing dialogue with PACS providers are essential to ensure they are appropriate and compatible with a customer's clinical practice. The main questions he said users should ask are: 'How and where will I use these tools in my workplace?' 'Are these tools clinically relevant for my population and clinical images.'

'In mammography, we know the images aspect might change, given the different characteristics of devices from different vendors (i.e. detector, angle, processing algorithms, etc.). An algorithm might suffer from these changes.'

Gubern-Merida has no doubt that BC screening is where AI matters. 'It's where women can benefit the most,' he concluded. 'AI tools are already there to help radiologists in clinical practice. But, we need more studies to validate the best approach to obtain the best out of it.'

Dr Gubern-Mérida gained his joint PhD degree in medical imaging at the Diagnostic Image Analysis Group (DIAG) of the Radboud University Medical Centre in Nijmegen, the Netherlands and the University of Girona in Spain. His research focused on automated analysis of breast MRI, by developing image analysis and machine learning algorithms to detect breast cancer. As a post-doctoral researcher at DIAG he expanded his research to other breast imaging modalities (mammography, digital breast tomosynthesis, and automated 3-D breast ultrasound). In 2016, he joined ScreenPoint Medical, and currently heads Research and Development, focusing on the continuous evolution of AI technology.

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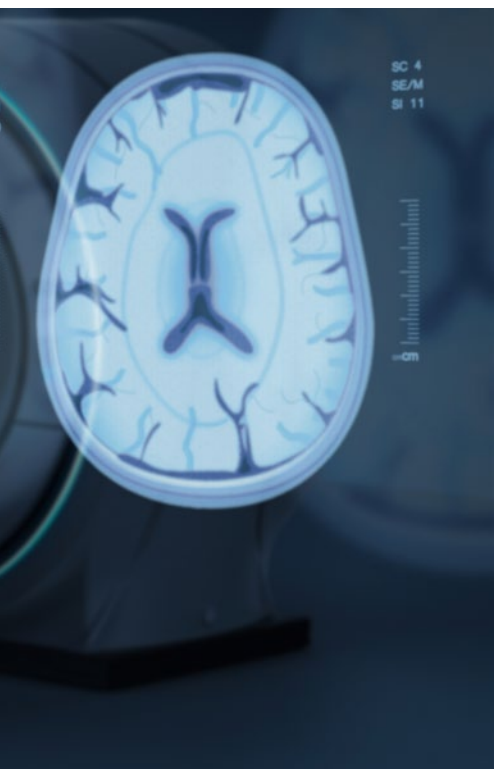


or reviews. The idea is to highlight the most relevant teaching cases to the current case, and then make the link with an encyclopaedia or radiology assistant to broaden knowledge.

It will be key to understand why AI systems think which cases are relevant, Kotter pointed out. 'Usually, deep learning is a black box and you don't know how it works. But, in order to learn how AI systems work, AI systems must become explainable.' One way could be to measure similar cases from an existing database.

Run in the background, AI could help radiologists detect gaps in their reading and recommend personalised strategies – for example, read more cases for gastroenterology tumours.

The impact on management

There are many staff shortages compared to the high image data volume to interpret. Time-consuming radiology services are increasing, fuelled by sub-specialisation and 24/7 services needed. Many promising solutions are available, according to Professor Christoph Becker, at the Radiology Department, Geneva University Hospital.

'Automation of our departmental workflow is probably the lowest hanging fruit to help us. But there is also automation of time consuming and repetitive visual tasks, particularly those with high volumes and low complexity. Automation of data management will help us to extract data from patient records, so that we don't have to do it manually and may be able, in the future, to access the current scientific literature data mining related to the cases we are reading,' he said.

However, stopping radiology residency programs now would have unknown consequences. 'We supply the radiologists for Western Switzerland and have 11 subspecialised units just in our department. This would deplete rapidly if we did not replace older radiologists who retire,' Becker reasoned.

Should training stop, many unsolved questions would arise, such as where and when to buy machines and robots, ideally with board certification and ESR level 3 subspecialty skills? Who would override the wrong decisions in the meantime? Are machines and robots acceptable as imaging consultants for difficult, complex cases? What would patients say? Who would take the medico- legal responsibility – robots or firms that supply them?

Anxiety about potential future displacement is discouraging medical students to choose radiology as a career, a Canadian survey shows. 'We must address those fears,' said Becker, who outlined five immutable elements to manage complex change: vision, skills, incentives, resources and an action plan. 'If vision is lacking, confusion will result. If skills are lacking in your department, there will be anxiety. Lack of incentives will cause resistance in staff. Resources may be missing and cause frustration. And, if you have no action plan, or it's not clear, downfalls are guaranteed.'

To integrate AI smoothly, people must decide what to automate and if it makes sense for their institution. 'A fool with a tool is still a fool. Besides, when is a tool mature for clinical routine? One must design a roadmap and steps to take. What cannot be measured cannot be managed,' Kotter emphasised.

Radiologists have lived with disruptive change for decades. Changing job descriptions have been the norm and technological progress demands constant updating of skills. Rads have also been pioneers in many developments, including PACS integration – which almost never happened.

'We're used to revolutions in imaging. PACS was a revolution. We had many meetings about it and it took 20 years to become clinical routine,' Kotter said, concluding: There's also a Valley of Death of radiology, and many projects don't make it to the work place.'

Elmar Kotter MD MSc gained his Medicine and Computer Science degrees at Montpellier University (France) and Université René Descartes in Paris. From 1993-2000 he was radiology resident in Freiburg University Hospital, Germany, where, from 1994, he directed the Freiburg PACS-Project. From 1997 he headed IT in the radiology department and became its vice chairman in 2003. and, in 2008, became Associate Professor of Radiology at the University. He chaired the IT working group of Germany's society of radiology (2006 - 2015). He is also vice-president of the European Society of Medical Imaging Informatics (EuSoMII), as well as a member of the Subcommittee on eHealth and Informatics for the European Society of Radiology.

Spanish hospital coordinates €10 million EU project

Aiming at lethal paediatric tu

La Fe University and Polytechnic Hospital in Valencia, Spain, is coordinating EU-funded program PRIMAGE, which uses precision information from medical imaging to advance knowledge of the most lethal paediatric tumours, by establishing their prognosis and expected treatment response using radiomics, imaging biomarkers and artificial intelligence (AI), Mélisande Rouger reports.

About six months ago, the European Commission funded the PRIMAGE* project with over €10M, to help improve treatment and identify a tumour's main characteristics without the need for biopsy, using computational processing of medical images on the cloud.

The PRIMAGE consortium will create a bank of images obtained through AI, using an open cloud-based platform to support decision-making in the clinical management of Neuroblastoma (NB), the most frequent solid cancer of early childhood, and Diffuse Intrinsic Pontine Glioma (DIPG), the leading cause of brain tumour-related death in children. The PRIMAGE platform will implement the latest advancement of in-silico imaging biomarkers and modeling of tumour growth towards a personalised diagnosis, prognosis and therapies follow-up.

The ambitious project involves 17 European partners, including several internationally recognised institutions, and four leading industrial partners, all of which are working under the aegis of the Imaging Biomedical Research Group (GIBI230) at the La Fe Research Institute in Valencia.

The PRIMAGE project team

The great value brought by PRIMAGE is that the study will use real world data as a foundation to help identify the best treatment for each individual patient, instead of collecting sample data, as in prospective trials. Exploiting the information from existing imaging biobanks and patient clinical files using advanced computational methods will help significantly to improve decision making in cancer management, according to GIBI 2030 Director Luis Martí-Bonmatí, Chairman of Radiology at La Fe Hospital.

Predicting disease right at the beginning

'Using real world data in in-silico models can help establish imaging and molecular data's capacity to estimate and predict right from the beginning of disease, to ultimately make the best therapeutic decision for each patient. This has, to our knowledge, never been done before for any type of cancer in a multicentric approach and using such disruptive technology,' Martí-Bonmatí said.

Being able to precisely estimate tumour phenotype, aggressiveness, stage and extension, define the best treatment plan and establish the most accurate prognosis will definitely help paediatric oncologists improve their decision-making, he added.

PRIMAGE will use the latest available technology in the field of computing and AI, for example machine learning software developed by QUIBIM, a spinoff of La Fe's Research Institute that has received CE marks for its image

Methods, quality assurance and commercial providers issues

Molecular testing

In terms of success in revolutionary cancer treatment, molecular genetic examination procedures have developed immensely over recent years. They now range from conventional polymerase chain reactions (PCR) or fluorescence-in-situ hybridisation (FISH) to Next Generation Sequencing (NGS) with analysis of the entire exome or genome (Whole-Exome, WES or Whole-Genome, WGS) and of the transcriptome (RNA-seq) within genetic diagnostics. Here, Professor Wilko Weichert MD, Director of the Institute of General Pathology and Pathological Anatomy at the Technical University of Munich, outlines methods, quality assurance and the role of commercial providers in molecular testing.

'Fundamentally, conventional in-situ protein analysis is still very important in predictive diagnostics. In part, it has been carried out for decades and is therefore backed by a wide range of data,' Professor Wilko Weichert points out. 'Now, along with protein expression analysis, genomics, i.e. sequencing for the detection of mutations, is playing an increasingly important part, often in the shape of multigene analysis, for example. This is currently the backbone of molecular diagnostics.'

Challenges for molecular testing

Weichert emphasises that, despite the increasing differentiation and diversification, molecular diagnostics is no end in itself but an integral part of treatment planning. 'What use would the best molecular profile of a tumour be if it does not result in any clinical consequences? We have to tailor molecular diagnostics in such a way that it generates information that can be used for therapeutic purposes in the best possible way.' This is a technological challenge. 'Complex molecular assays in high-tech patient care originally came from the world of biological research,' says the pathologist. 'Their use in medical diagnostics however calls for different qualitative benchmarks, as we must never be wrong.'

In the case of solid tumours, the integration of molecular diagnostics into the entire diagnostic algorithm ensures a choice of the most suitable molecular verification procedure for a problem. According to Weichert, 'Very different assays can be used for this purpose. Their use also depends on the local environment in which the doctors work and on the expertise available to carry out genetic testing with the respective technologies.

Verification of molecular changes of importance in malignant tumour development can be utilised for therapy

'The financial feasibility of modern molecular diagnostics in healthcare is currently another impediment.

'Fact: As doctors and scientists, we are repeatedly faced with situations where, from a purely theoretical perspective, we could offer something diagnostically, but for reasons of affordability it's just not possible for certain clinical situations,' Weichert explains.

Based on the understanding of scientific medical societies, the costs of molecular analyses, as long as they are specifically for measures of prevention, screening and assurance of diagnosis and/or treatment, must be covered by the cost bearers. In view of fast knowledge growth not only the unified assessment standard (EBM) for out-patient care must be reviewed regularly, but the new examination and treatment procedures (NUB) must also be adapted for in-patient care.

'Financing is a particular problem in Germany due to the differentiation between outpatient care and hospital care with all its in-patient flat rates. If a new treatment procedure is beneficial for a patient, but not particularly cheap, these flat rates create funding shortfalls. For example, the diagnostic process for critically ill patients is then transferred from in-patient to out-patient care, where the treatment can be funded without putting extra pressure on the flat rate per case system in hospitals. This leads to unnecessary delays in the treatment process.'

Quality assurance is the be-all and end-all

Quality assurance in molecular pathology is extremely important. 'The German national Accreditation Body ensures excellent monitoring of quality standards in pathology,' Weichert says. 'Around 100 pathologies have been accredited based on a very strict system; this also includes 40 for molecular pathology. They are basically reviewed on an annual basis. 'This first cornerstone of quality assurance is complemented by a second one in the shape of its own company: The Quality Initiative Pathology of the German Society for Pathology. 'This subsidiary of the German Society for Pathology and the Federal Association of German Pathologists carries out numerous ring trials which molecular diagnostic institutes, for instance, can and must participate in if they want to become accredited.'

At the end of any diagnostic procedure comes an interdisciplinary discussion about patients by a tumour board, to agree on therapy recommendations. 'We need experts in molecular diagnostics in all regions; pathologists are part of tumour boards and make essential contributions to therapy recommendations with their expertise,' Weichert points out. In recent years molecular tumour boards with particular expertise in the interpretation of molecular-diagnostic results have developed. These also work interregionally. 'We will probably have a multistage system in Germany that's structured into levels of complexity because not all German pathologists will be able to offer the same level of highly complex molecular diagnostics. The procedures are already too complicated for this, and, if you only have a few cases to work on, also too expensive, he believes.

The problem with commercial providers

The use of commercially orientated molecular diagnostics in treatment is viewed critically by the specialist societies. They fear a development as seen in the USA: 'Commercial providers have discovered large-scale provision for themselves,' Weichert observes. In the USA, several private laboratories have been set up by exclusively commercial companies to carry out sequencing. Pathologists send in their tissue samples and receive a written molecular diagnosis. This became possible as comprehensive regional care entailing this type of complex analytics was not possible via the healthcare providers.

These companies are expanding globally and trying to integrate their business model into the existing German system – a system which, unlike in the USA, is comprehensively structured with high expertise. 'A cuckoo's egg, as the technical,

mours

post processing algorithms and is in charge for developing the PRIMAGE platform's architecture, adaptation and design.

Knowledge acquired will benefit cancer

Cancer remains the first cause of non-traumatic death among children, but it has a very low incidence in this populations. Experts estimate that 500,000 EU citizens will be paediatric cancer survivors by 2020.

Neuroblastoma is the most common extracranial tumour in children and represents 8-10% of all paediatric cancers. In Europe, 35,000 new cases are diagnosed each year, 1,000 in Spain alone.

Diffuse Intrinsic Pontine Glioma is a very rare disease in childhood and is associated with low survival (10%). There do exist palliative treatments and some research going on, but there is no curative treatment as yet.

PRIMAGE's scope on these two diseases is expected to shed light on two of the less documented cancers. 'Cancer is more rare in children than in adults. It is pertinent to use the data from international imaging biobanks in this setting, because we wouldn't get many cases locally. Because there are so few reported cases, paediatric cancer tends to be forgotten by research, which makes it another interesting challenge for us, especially at La Fe Hospital, which is a European reference centre for neuroblastoma and DIPG,' Martí-Bonmatí said.

Due to the peculiarities of computational approximation in these two types of tumours seen in childhood, investigation done in this area will also be applicable to other tumour types, to help advance research on cancer in general.

'Our big interest is to give importance to real world data. If we're successful, the tools and methodology used in PRIMAGE can be extrapolated to other cancers and improve knowledge and decision-making in this setting as well,' Martí-Bonmatí concluded.

* PRedictive In-silico Multiscale Analytics to support cancer personalised diaGnosis and prognosis, Empowered by imaging biomarkers (PRIMAGE)

Dr Martí-Bonmatí is Chairman of Radiology and Director of the Medical Imaging Department at La Fe University and Polytechnic Hospital, Valencia. He is full member of the Spanish Royal National Academy of Medicine representing Radiology, and was founder and Director of the Research Group on Biomedical Imaging (GIBI230) within La Fe Health Research Institute. He also co-founded QUIBIM (Quantitative Imaging Biomarkers in Medicine), an innovative spin-off company from the Research Institute, although he no longer has a relationship with the company. He has been President of the European Society of Magnetic Resonance in Medicine and Biology (ESMRMB), Spanish Society of Radiology (SERAM), Spanish Society of Abdominal Radiology (SEDIA), and European Society of Gastrointestinal and Abdominal Radiology (ESGAR).

Wilko Weichert MD is Professor (W3) for Anatomical and Surgical Pathology, and Chairman of the Institute of Pathology, at the Technical University Munich. In his translational tumour research, the professor (author of over 370 original peer reviewed articles), focuses on tissue-based molecular pathology to establish novel predictive, prognostic and diagnostic biomarkers as well as novel therapy targets in solid human tumours. The specific focus is on gastrointestinal, pulmonary, pancreatic plus head and neck carcinomas – he is past-president of the Head and Neck Working Group of the German Society of Pathology.

molecular-genetic service is taken out of the treatment process and the associated clinical services, such as the discussion of results, and interpretation by tumour boards, must still be provided locally but are not reimbursed,' Weichert explains.

A further disadvantage is the loss of data sovereignty and the transfer of molecular-genetic patient information. 'As clinicians, we transfer medical data to a private company paid to work with it. This can lead to situations where some companies not only offer the diagnostic procedures but also produce the respective medication, and this is not a favourable constellation. Health data on the whole is big business.' (bs)

High-throughput screening advances

Acoustic mist ionisation mass spectrometry

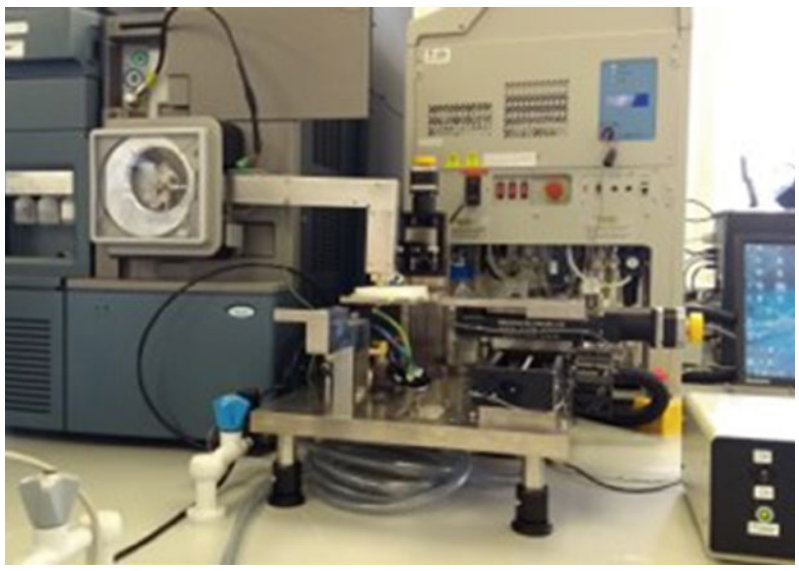
Report: Mark Nicholls

Acoustic mist ionisation mass spectrometry (AMI-MS) has played a pivotal role in the evolution of high-throughput screening (HTS) and steps are being taken to advance this field to other potential applications. AstraZeneca has been an important player in this area, having already run more than 10 full collection HTS campaigns against a range of enzyme target types. The company is now working on future applications, such as cell screening.

The work to date, and future applications, was outlined by the biopharmaceutical company's Principal Scientist Dr Jonathan Wingfield during SLASEurope 2019, in the presentation 'Continued Development of AMI-MS for High-Throughput Mass Spectrometry Applications Beyond Biochemical HTS'.

Wingfield told the congress – which revealed recent developments in instrumentation, assays, and diagnostics – how AstraZeneca has started to explore cell-based applications with AMI-MS. He illustrated this development with data generated from HepG2 cells comparing the mass spec 'fingerprints' from cell lysates.

So far, AstraZeneca has tested a library of compounds with known liver damage mode of action, and in several cases showed the modulation of metabolites by compounds, which is consistent with the mechanism of action of these compounds.



An AMI-MS system offers potential for future applications such as cell screening

For the AMI-MS work a standard Echo 555 transducer, which had been externalised, was used to provide the acoustic tone burst to the 384-well plate, which generates the spray event of multiple 50-100fL droplets.

Above the plate, the team has a charging cone which pushes charge into the test well. The charge sets up a polarity gradient in the well and results in pre-charged droplets being formed as the acoustics fires; the charged droplets are pulled into the MS via a heated transfer line.

The speed of the acoustics enables samples to be loaded at a rate of three per second and, as it is contactless, there is no risk of cross contamination between samples.

The lab team note that speed and sample volume are key strengths of the system and, as only a small volume is sampled, there is always the opportunity to re-read a well if necessary.

Dr Wingfield said that AstraZeneca has had considerable success with biochemical HTS despite suppression being an issue and, at times, limiting sensitivity. However, he added that since the biochemical assays are run using substrate concentrations typically in the µM range, there has usually been enough sensitivity to measure both substrate and product.

With the system running on a time-of-flight MS all the signal peaks relating to their assay were visible and, in terms of cellular applications, there was the ability to generate 'fingerprint' spectra from lysates.

'This technology enables us to work with small numbers of cells and the ability to sample multiple times means we can generate significant technical and biological replicates to improve the confidence we have in the data even when the analyte signal is low,' he said.

From a workflow perspective, the assay is built in the plate and fired directly from the plate into the MS, so there is no requirement for complex re-plating or additional sample preparation post assay.

AstraZeneca believes the cell lysate work has the potential to open up new areas of application.

Low cost and robust

AMI-MS is the hyphenation of a Waters Xevo G2XS time-of-flight (ToF) mass detector with an acoustic sampling interface. This new technology enables direct injection of samples from a standard 384 well plate into the mass spectrometer at very high-throughput making the workflow process relatively simple as the assay reagents are assembled in the one plate which then is passed to the MS to read.

As the automation requirement for AMI-MS is minimal and simple, Wingfield indicates that makes it relatively low cost and robust.

In addition to building the hardware, there has been a significant investment by AstraZeneca in data and data analysis and handling workflows, which enable HT analysis alongside a collaboration with GeneData and its Expressionist software to automate data analysis.

This, said Wingfield, has significantly reduced the analysis time from hours to minutes for a typical HTS batch of data and the ability to analyse data in close to real time.

Dr Jonathan Wingfield is Principal Scientist in Discovery Sciences, R&D, AstraZeneca, Discovery Sciences, based at Cambridge in the UK. He joined AstraZeneca in 2000 as part of a team responsible for delivering automation solutions and technology into the disease area of post high-throughput screening. He was later involved in using leading edge technology to deliver high quality data to global projects, including delivery of acoustic droplet ejection technology.

LC-MS for the clinical laboratory

Finding the right solution

LC-MS has established itself as a powerful tool for clinical applications. However, for maximum utility, it is important that laboratories develop a comprehensive understanding of the available platforms and options.

Report: Dr Debadeep Bhattacharyya[1]

Advances in liquid chromatography (LC) and mass spectrometry (MS) instrumentation have seen the popularity of LC-MS grow rapidly. A wide range of component technologies now exist, from single quadrupole* and triple quadrupole (QqQ) mass spectrometers, to the use of Thermo Scientific Orbitrap systems with high resolution accurate mass (HRAM)** capability. Similar improvements in high-performance LC (HPLC) technologies mean that the analytical power of LC-MS has kept pace with the need for better selectivity and specificity, greater throughput, automation, and most importantly, increased confidence in results.

LC-MS as a clinical tool

The power of LC-MS is illustrated by its growth as a key tool for clinical analysis. The improved specificity and selectivity of LC-MS compared to immunoassay techniques, its ability to analyse multiple analytes in one run, as well as the lack of dedicated immunoassay kits for certain analytes and the variability observed for some available immunoassays, have all contributed to the uptake of LC-MS in clinical use. LC-MS is now routinely used for a wide range of clinical applications, from the quantitation of Vitamin D (and its analogues) and therapeutic drug monitoring assays, to the quantitation of immunosuppressants and toxicology/endocrinology assays. Today, clinical laboratories looking to adopt LC-MS have three potential options:

- Turnkey solutions that incorporate instrumentation, software and complete assay kits provided by the manufacturer
- Platforms that enable commercially available and validated LC-MS methods
- Platforms that run laboratory developed tests (LDTs)

Inserting the reagent rack into the Thermo Scientific Cascadion SM Clinical Analyser***

*** Product is IVD/CE marked but not 510(k)-cleared and not yet available for sale in the U.S. Availability of the product in each country depends on local regulatory marketing authorization status.

In the latter case, the development and optimisation of LDTs require extensive verification and validation steps. However, for many laboratories, the abundance of technologies and system configurations means the challenge often starts well before LDT optimisation begins.

Meeting laboratories' needs

The list of medical devices available for LDTs is rather small compared to the LC-MS instruments available for clinical research; choosing the optimal combination of platforms is still not an easy task. The desired platform should offer:

- Quality data across a range of biological matrices
- Reduced instrument downtime to minimise costs per sample
- Fast turnaround times to ensure high productivity and rapid reporting of results
- Ability to address high throughput sample requirements
- Ease of operation regardless of user expertise

Whilst most laboratories will strive to deliver against all these criteria, they may prioritise some needs over others. For example, some laboratories will desire LC-MS set-ups that offer the flexibility to develop multiple methods, whereas others require high-throughput workflows capable of analysing hundreds of samples each day for a specific analyte. Similarly, some laboratories have the expertise to address complex clinical assays with LC-MS, while others would appreciate a fully-automated workflow from sample preparation to report generation.

[1] Dr Debadeep Bhattacharyya is Senior Marketing Manager for Clinical and Forensic Applications at Thermo Fisher Scientific.

*For research use only.

**For in vitro diagnostic use.

Efforts to reduce nosocomial infections.

A&E Staphylococci POCT

Martin Möckel and Dorothee Riedlinger, from the Charité Medical University Berlin, Emergency and Acute Medicine Campus Virchow-Klinikum, and Campus Charité-Mitte report on POCT testing in the A&E department to screen for Staphylococcus aureus colonisation of the nose or throat.

Report:
Walter Depner

People colonised with Staphylococci are at increased risk of developing a nosocomial, i.e. hospital acquired infection (HAI), the origin of which will be endogenous – i.e. the patient's own disease reservoir. Colonisation with staphylococci is common: 20-30% of the healthy population is colonised by Methicillin-sensitive Staphylococcus aureus (MSSA), 2-3% are colonised by Methicillin-resistant Staphylococcus aureus (MRSA).

Figures on the prevalence of nosocomial infections are based on estimates. An annual 2.6 million nosocomial infections are estimated to occur within the EU, with 400,000 - 600,000 of those arising in Germany. The presence of nosocomial infections leads to extended hospital stays and treatment in intensive care, as well as to around 90,000 deaths a year across Europe.

Patients suffering from acute illness are admitted to the hospital via A&E departments. The prevalence of Staphylococcus colonisation amongst those admitted via A&E is not known upon admission. However, along with acute treatment, preventive treatment, which would improve overall healthcare, can be offered in the A&E department as well. Based on this hypothesis, it was examined whether a POCT hospital admission screening system for nasopharyngeal colonisation by Staphylococcus aureus in A&E is feasible.

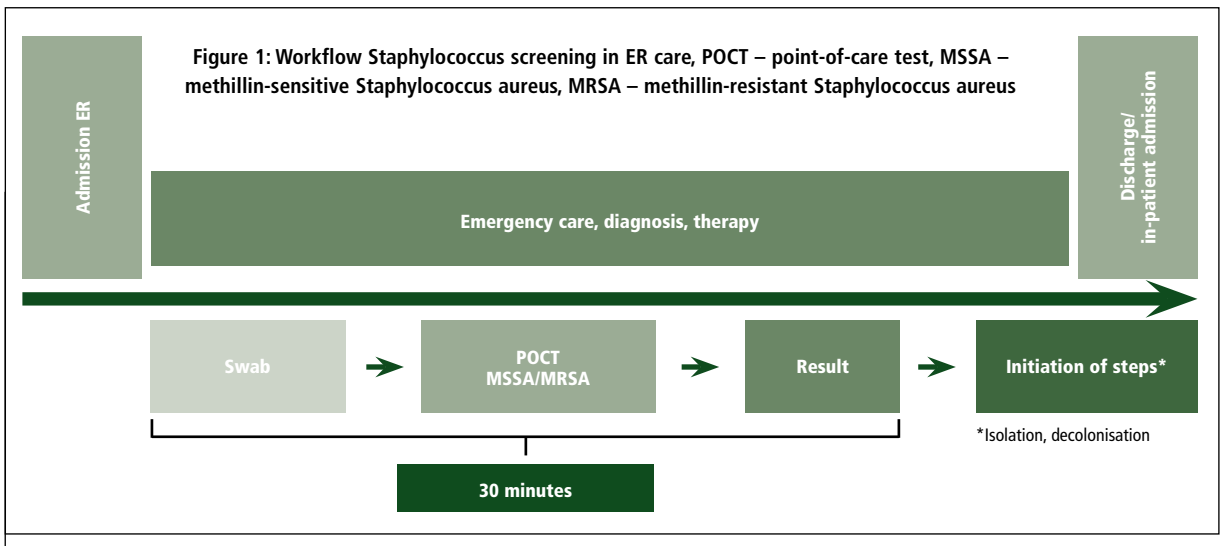


Figure 1: Workflow Staphylococcus screening in ER care, POCT – point-of-care test, MSSA – methillin-sensitive Staphylococcus aureus, MRSA – methillin-resistant Staphylococcus aureus

102 cases were examined

A&E nurses took nasopharyngeal swabs from all patients admitted to our large, inner city A&E department, irrespective of whether they were seen for out- or in-patient treatment. 102 consecutive, non-selective cases were examined using the POCT system. (The examinations were carried out using a prototype of the MSSA/MRSA-assay of the cobas LIAT system from Roche). 26.4% of these swabs tested positive for colonisation with MSSA; three swabs tested positive for MRSA. In only one case had MRSA colonisation been previously described. It was possible to integrate this screening into the A&E admission process without delay.

Body part	Percentage of Staphylococcus colonisation, population at large	Percentage of staphylococcus colonisation, nasal carriers of staphylococcus
Nose	27%	100%
Hands	27%	90%
Skin (thorax, abdomen)	15%	40-45%
Perineum	22%	60%

Figure 2: Staphylococcus colonisation by body part. Adapted from Wertheim et al. Lancet Infect Dis 2005; 5(12):751-62

In the second step, nasopharyngeal swabs were taken from 1,000 consecutive patients and examined for the risk factors for MRSA colonisation, as detailed by the Robert-Koch-Institute. In this cohort, 30.4% of patients were colonised by MSSA and 2.7% were colonised by MRSA. Based on their anamnesis, only 26.1% and 59.3% respectively of those examined were at an increased risk of colonisation with MRSA, which would have called for routine screening.

Early screening exams with fast/easy test systems

These examinations show that the cohort of those admitted to A&E have a rate of Staphylococcus colonisation similar to that described above, which indicates that early screening examinations in the context of acute care provision with fast and easy test systems is possible.

As the existing factors for risk determination only capture a part of colonised patients, it makes sense to look at other criteria for screening examinations. One option is that certain illnesses and treatments which, in turn, have a higher risk of nosocomial infections – such as invasive mechanical ventilation, emergency surgery or severe infection – should automatically involve screening and specific follow-on procedures, such as decolonisation treatment. Further analysis is required to determine which patient collectives should benefit from early screening, and studies should confirm the benefit of preventive measures, such as decolonisation treatment to reduce nosocomial infections.

The objective is to reduce the prevalence of nosocomial infections through early, specific preventive measures.

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Dorothee Riedlinger is Scientific Assitant in the Emergency and Acute Medicine Campus Virchow-Klinikum, and Campus Charité-Mitte Berlin, Germany

Martin Möckel MD is a Senior Physician, Professor of Cardiology and Head of Emergency Medicine and Acute Cardiovascular Care at Charité, University Medicine Berlin, Germany. He is also an Adjunct Professor at James Cook University, School of Public Health and Epidemiology, Townsville, Australia. The professor's research focuses on biomarkers, healthcare in emergency and acute medicine and the implementation of interventional therapy in acute coronary care. He has led a number of multicentre trials. Martin Möckel is also part of the biomarker core groups of the Acute Cardiovascular Care Association and the 2019 congress president of the German Society for Internal Intensive Care and Emergency Medicine.

ERRATUM

LABBook 2019

Please accept our publisher's apology for the following error on page 20:

Sentinel, a Sysmex company – Sentifit 270

Sentinel CH. SpA is **not** a Sysmex company.
Sysmex Europe GmbH distributes Sentinel products, such as Sentifit 270.
Correction:

Sentinel – Sentifit 270 (Sysmex)

Criteria	LDTs	Assay Kits
Comprehensive workflow	Ability to optimise parameters of each component of the platform (sample prep, LC and MS)	A fixed design with all components as part of a single analytical platform
Platform flexibility	Choice of HPLC and tandem MS	Fixed system combination
Method flexibility	User decide their LDTs	Menu of assays is set and validated by the manufacturer
Sensitivity range	Depends on the QqQ	Limited flexibility as the mass spectrometer cannot be changed
Cost per sample	Can be optimised by changing sample prep protocol, LC and tandem MS	Typically fixed for a listed method
Throughput capability	Varies from standalone UHPLCs to multiplexing capabilities with up to four channels	Dependent on need; up to two LC channels per mass spectrometer
Ease-of-use	Requires training/some knowledge of MS	Turnkey simplicity; one platform for sample prep, LC and MS
Desired expertise	Rudimentary knowledge of LC-MS required	No prior knowledge of LC-MS required
Sample turnaround time	Facilitated by the fastest QqQ and UHPLC systems on the market Users can optimise time to results based on their requirements	Due to random access workflow, ensures faster path to results from the sample receipt time
Analyte Types	Suitable for small and large molecules	Focused on small molecules
Software	Integrated with the LC-MS system	One software for the entire workflow
Report generation	Customised template; can be automated	Customised template; automated
LIS compatibility	Managed by an interface (third party); compatible with any LIMS	Bi-directional connection via ASTM IT protocols

Making the right choice - The solutions available to clinical laboratories fall into two main categories: Class I medical devices for LDTs and Class II clinical analysers equipped with assay kits. Different platforms will offer different benefits, as highlighted in the table. (Details: https://www.thermofisher.comw

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