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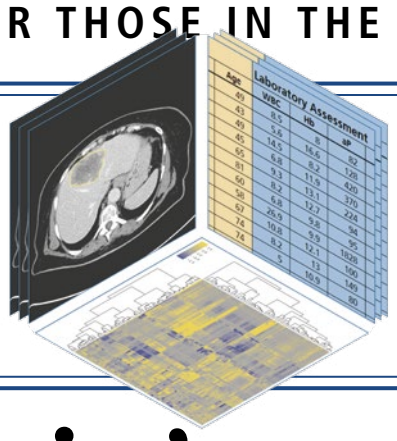

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The 'bionic' radiologist

Three steps towards healthcare improvements

Marc Dewey is Heisenberg Professor of Radiology, Vice-Chair of Radiology at Charité – Universitätsmedizin Berlin, Germany, and he presided over the Berlin Röntgen Society from 2011 to 2013. He received the Röntgen Award in 2009 and the Curie Ring in 2012 – the German Röntgen Society's two highest scientific awards. Dewey was also secretary of the 2011 German Röntgen Congress.

Professor Marc Dewey, Vice Chair of the Department of Radiology at Charité – Universitätsmedizin Berlin, made value-based radiology the main theme of the Wilhelm Conrad Röntgen Honorary Lecture during ECR 2018. Radiology practice needs change, he said, and radiologists should grasp at new technology to drive their future. His lecture was summarised in a recent comment in The Lancet. See Link: www.thelancet.com/journals/lancet/article/PIIS0140-6736%2818%2931193-0/fulltext

Report: Sascha Keutel

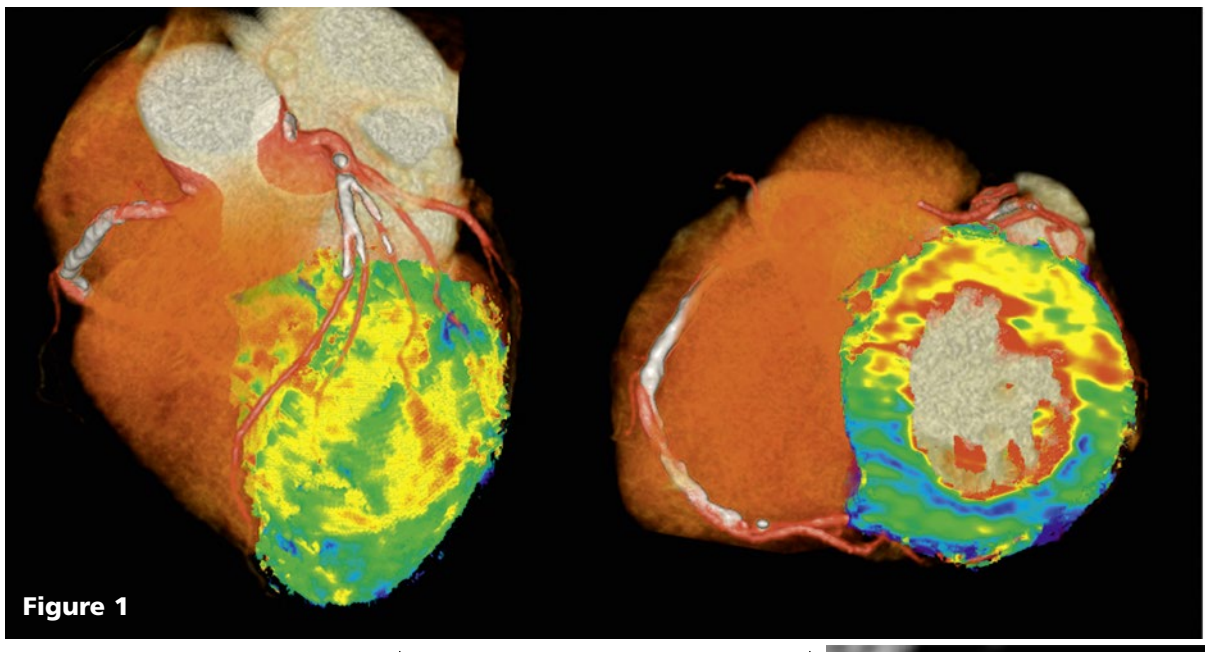


Figure 1

4D-CT perfusion images of the heart (Dr. Kakuya Kitagawa and Prof. Marc Dewey)

Dewey's lecture presented a list of issues regarding current healthcare systems. Among foremost patients' complaints on hospital admittance is being asked about their medical history multiple times from different staff members or departments.

Also, patient care services that decide the clinical strategy and tests to be made have conflicts of interests and different aims. 'We're not using evidence-based approaches to make those decisions,' Dewey said.

Additionally, the idiosyncratic terminology in radiologists' reports prevents major critical findings from being detected. According to Dewey, a recent study on determination and communication of critical findings in abdominal imaging found that one-third of it went undetected. (https://www.ncbi.nlm.nih.gov/pubmed/19581643).

A vision of the future

Dewey spoke of a Commonwealth Fund study that concluded that increasing healthcare spending per GDP does not equate to better patient outcomes, or the performance of the healthcare system measured by equity and accessibility. Reality: the more money nations invest in their health care system, the worse the outcome in terms of performance is – a really dramatic result and reason to introduce value-based medicine in radiology, he said. The general goal of value-based radiology is to improve patient outcome with lower cost. 'Sometimes that means doing less – especially less imaging.'

Value-based radiology, he believes, will gain a central role in addressing three issues:

1. Improving personalised decision-making about if, when, and which patients need diagnostic imaging
2. Increasing consistency in how images are acquired and interpreted by the 'bionic' radiologist
3. Enhancing the link on findings and reports with treatment recommendations and management decisions.

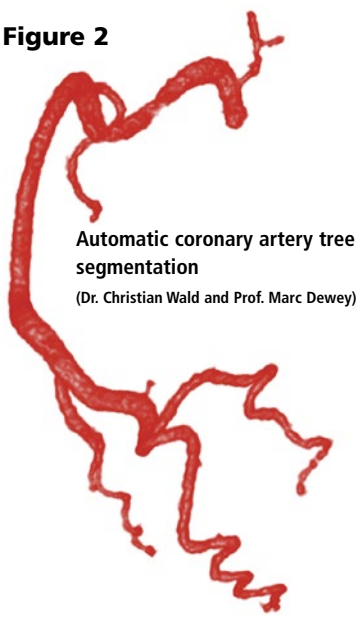
Evidence-based decisions

First: Decision support tools, based on evidence, could help to overcome too much imaging in the wrong patients. AI tools would allow better predictions and free up radiologists' time to talk to a patient. This needs a patient's data integration with decision support tools, such as the European Society of Radiology's iGUIDE and eGUIDE.

The bionic radiologist

Second: The integration of AI with human efforts – the 'bionic radiologist' – has great potential to increase consistency in radiological image analysis and reduce errors.

Figure 2

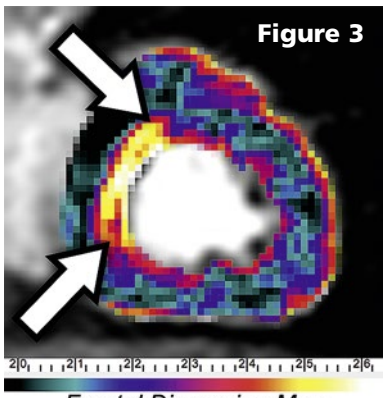


Automatic coronary artery tree segmentation (Dr. Christian Wald and Prof. Marc Dewey)

Dewey foresees a human doctor using a device to gain an automated analysis and then interpreting the results and strategies along with a patient. An existing example is 4D-CT of the heart, which produces three billion voxels for a single patient (Figure 1). Patients can't hold their breath for long, so there's heart and lungs motion. Can we manually adjust? Can we go through these three billion voxels? That's very hard to achieve.' Dewey then explained that radiologists need automated approaches that do registration and pre-processing before a doctor even begins. Figure 2 shows such a pre-processing example of automatic coronary tree segmentation based on 3D cardiac CT.

The bionic radiologist makes use of automated pre-processed data, e.g. using fractal analysis (https://www.ncbi.nlm.nih.gov/pubmed/27436024) while still being the major interpreter and integrator of the data (see Figure 3). This combined approach to leverage both the consistency of automatic analysis and individual interpretation of human image analysis 'is a paradigm shift,' Dewey said.

Figure 3



Fractal analysis of myocardial MR perfusion imaging. Fractal analysis has been established as a method to differentiate obstructive coronary artery disease and microvascular dysfunction. In this patient, a perfusion defect due to coronary artery disease with a fractal dimension of 2.47 is depicted (arrows) (Dr. Florian Michallek and Prof. Marc Dewey)

Linking findings to treatment recommendations

Third: Structured reports that combine audio-visual information linked to patient data make them searchable and analysable and therefore improve the reporting, Dewey believes. A study of pancreatic cancer imaging showed that the evaluation greatly improved with structured vs. non-structured reports (https://www.ncbi.nlm.nih.gov/pubmed/25286323). Dewey concludes that structured reporting improves the way radiologists' discuss a case with referring physicians and plan treatment.

Natural language processing may also help radiologists to avoid a possible culture shock when classic dictation vanishes. While the structure is captured by natural language processing, standardised dictation could continue, he suggests. This would make transition easier because, in the end, 'culture eats strategy for lunch'.

Challenges and conclusion

'Everyone wants to be an innovator, yet no one wants to change,' he said, adding that addressing cultural issues is also important in changing radiologists' practice.

But, for Dewey, the 'potentially greatest challenge is the half-life of clinical data'. A study on test order prediction tools found that the accuracy of data to predict inpatient orders has a half-life of only four months (https://www.ncbi.nlm.nih.gov/pubmed/28495350). As healthcare changes rapidly, researchers won't be able to use robust data older than five years. Thus, says Dewey, 'we don't need big data; we need good data!'

Success in the three listed areas will free the radiologist to participate more actively in patient care, where automated systems are not good (yet).

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Computers will support clinicians, not replace them

AI solutions aid diagnoses and therapy choices

Report: Cornelia Wels-Maug

Neuroscientist Lynda Chin MD, Founder and CEO of Real-world Education Detection and Intervention, has little doubt: 'Artificial intelligence to the rescue,' she proclaimed in her keynote address at the Artificial Intelligence and Machine Learning Summit, held in Las Vegas this spring. 'We need a system and analytics to interpret data!' she urged, despite being well aware that building a suitable algorithm, as well as training it to discover patterns and identify relationships, is a tedious task. 'We train an artificial intelligence (AI) system just as we would train a doctor', she explained and pondered, 'What is the equivalent of a residency programme for an AI programme?'

Global interest in AI

Work to derive actionable insights from ever-increasing data is the next logical step. Hence, self-learning algorithms and their underlying neuronal networks have become a major focus in software development.

As the development of AI is highly correlated with the availability of data, healthcare attracts a lot of AI activities. According to a study by Roland Berger of the strategy consultants and human venture capital firm Asgard, 'Artificial Intelligence – A strategy for European startups', the healthcare and FinTech industries together, after B2B services, attract most AI start-ups on a European and global level. Nonetheless, have those undertakings in AI, machine learning (ML) and deep learning effected improvements in healthcare on a larger scale?

Solving real problems

Although AI has become a buzz word in the healthcare world, its use is still in early days. AI is accredited with revealing clinical and operational insights and contributing to spare patients from unnecessary procedures and worry. Some examples on how AI enhances diagnostics and improves disease management include:

Picking up illnesses earlier

Ultromics, a new AI-based solution developed by Paul Leeson, Professor for Cardiovascular Medicine at the University of Oxford, diagnoses cardiac scans to determine a patient's risk of an imminent cardiological problem. Currently, cardiologists can defer from the timing of the heartbeat in scans if there is an impending cardiological problem. However, they are wrong in one in five cases, leading to patients being discharged and suffering a heart attack at home or having unnecessary surgery.

To train Ultromics, Leeson used the scans of 1,000 patients he had treated over the past seven years, along with information about whether those patients continued having heart problems. The solution picks up details in the images doctors cannot see and gives recommendations as to whether a patient should be treated further.

Ultromics has been tested in clinical trials in six cardiology units and, according to Leeson, the data indicates that the solution has greatly out-performed its fellow cardiologists. The trial results suggest further that Ultromics could save lives and spare patients unnecessary surgery, which Leeson reckons could save England's NHS more than £300 million per year.

Another example is an AI/ML-based system by the British start-up Optellium, which addresses the management of patients with large clumps of cells – nodules – in the lungs. According to Optellium, up to 30% of all patients scanned have such small nodules of which the majority are harmless. However, radiologists often struggle to determine if a nodule is cancerous, leading to an indeterminate diagnosis that needs up to two years follow-up imaging to monitor potential growth and, in some cases, the performance of biopsies and surgeries.

The solution, the firm reports, 'provides an objective risk score of nodule malignancy learned from a database of thousands of examples with known ground-truth diagnoses', enabling clinicians to 'confidently stratify lung nodule patients earlier, potentially on the basis of only one or two scans'. Optellium's chief science and technology officer, Dr Timor Kadir, reports that trials of the system in Manchester imply that more than 4,000 lung cancer patients a year, in the UK alone, could be diagnosed much earlier and hence have a much greater chance of survival.

Radiomics on the radar

The Fraunhofer Institute for Medical Image Computing (MEVIS) and partners are deploying radiomics to discover relationships between image features and clinical data within the Patient-Oriented Oncological Therapy Assistance (PANTHER) project. The aim is to develop a clinical decision support system for physicians to help determine the best course of therapy (medication, radiation, or a mix of both) for patients suffering from cancer of the colon or lymphoma. This will allow benefits to be maximised and curtail the side effects of a chosen therapy in a hitherto uncharted way by adjusting the course of prescribed therapy early in the treatment.

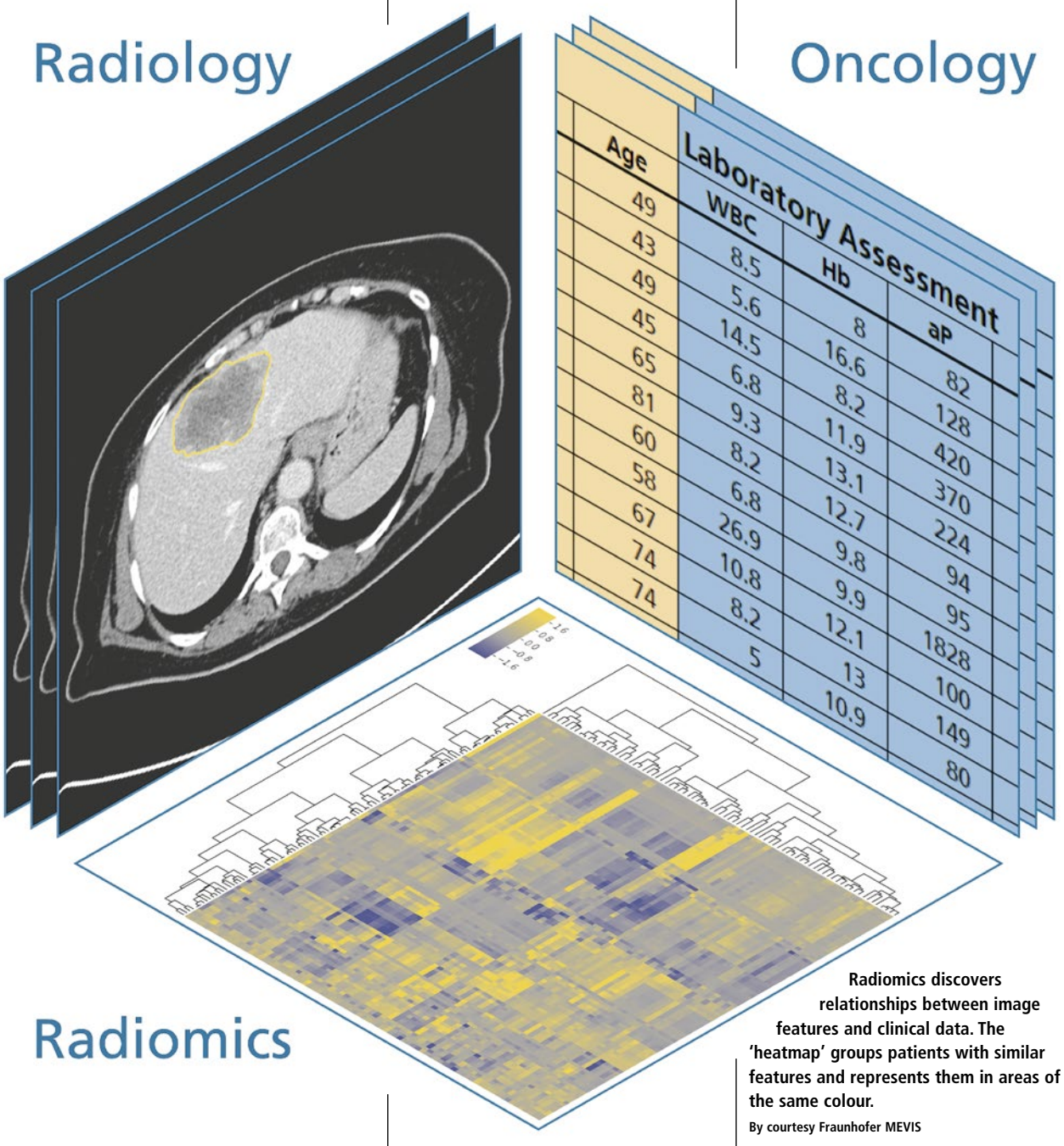
Jan Hendrik Moltz PhD, Research Scientist at Fraunhofer MEVIS, explained: 'So far, the size development of a tumour is the most important criterion in evaluating CT images. However, there is much more information hidden in those scans that has hardly been used.' He refers to information on changes in the shape and texture of a tumour that occur during therapy, but that cannot be detected by physicians with their bare eyes.

By deploying AI and deep learning on historical data from the Medical Centre of the University of Munich, it is hoped to reveal insights into the effectiveness of the therapy of bowel cancer and lymphoma.

Mid-term into the three-year-long project, Moltz reports good progress on homogenising the data, as well as segmenting computed tomography scans – segmenting refers to marking the structures to be analysed on the scans. 'Analysing the spleen, for example, manually, is very time-consuming,' Moltz explained. We have managed to develop a segmentation algorithm based on deep learning that is already so effective that it almost needs no further manual corrections. Automating the segmentation enables us to obtain outcomes much faster.'

The future role of the clinician

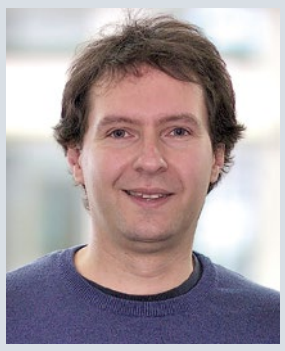
Last November, 'Xiaoyi', meaning 'little doctor', an AI-fed robot, successfully passed the medical approval test in China, even with above average results. Will this be the future? Chin shook her head: 'Data analytics helps healthcare to be more efficient, but AI is just a tool. It needs clinical experts to understand the problem. Although computers will make therapy decisions, they will support clinicians, not replace them.'



Radiomics discovers relationships between image features and clinical data. The 'heatmap' groups patients with similar features and represents them in areas of the same colour.

By courtesy Fraunhofer MEVIS

Paul Leeson, Professor for Cardiovascular Medicine at the University of Oxford



Jan Hendrik Moltz PhD, Research Scientist at the Fraunhofer Institute for Medical Image Computing (MEVIS).

Image: Fraunhofer MEVIS

Top Spanish innov

Tackling an anaesthesia

Report: Mélisande Rouger

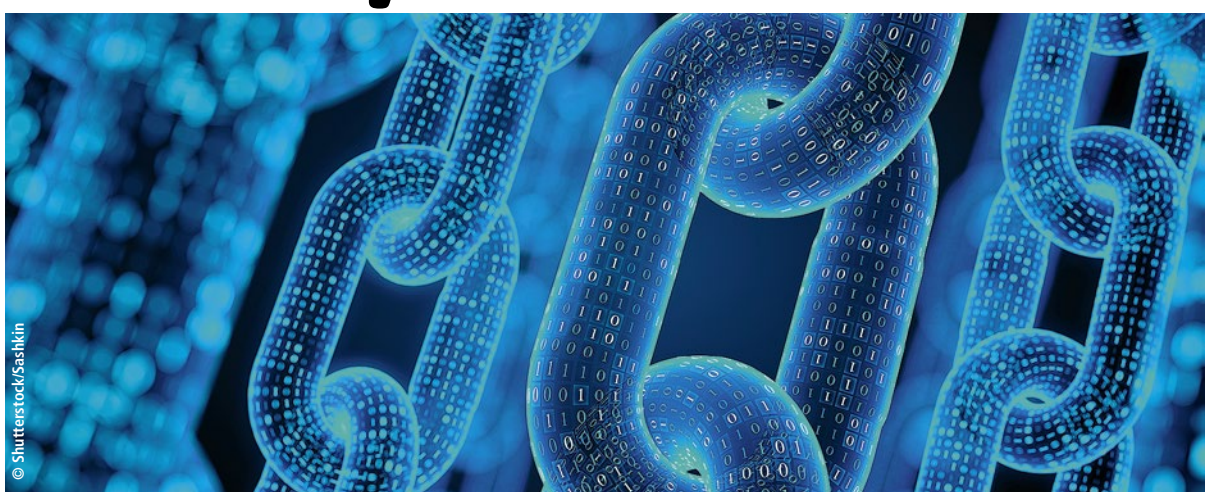
Four potentially game changing solutions selected for the annual commercial acceleration program of the Spanish foundation for innovation and prospective in healthcare (Spanish: FIPSE), included Duralock, a system that could ease post partum

Carlos García (left) led a team of anaesthetists and eng PDPH. A researcher at the Valencia foundation for healt among the Top 10 Spanish Talent list, which competed

"Hype will fade but the technology will remain"

A new way to handle data

A new dimension in data handling is not only emerging, but is already a reality in our lives. However, political discourse about this often lags behind real events. On behalf of European Hospital, Eva Britsch spoke with two experts who have an overview of clouds, decentralised data flows and the evaluation of personal data with IT help in various areas. Engineer Professor Alexandra Dmitrienko is a Secure Software Systems expert at the University of Würzburg, in Germany; Professor Bjoern Menze PhD is an IT expert at Munich's Technical Universit, particularly on health data.



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Prof. Bjoern Menze conducts research in the field of medical image computing. He develops algorithms that analyze biomedical images using models from computational physiology and biophysics. The emphasis of this work is on applications in clinical neuroimaging and the personalized modeling of tumour growth. He has organized workshops on medical computer vision and on neuroimaging at MICCAI, NIPS and CVPR, served as a member of the program committee of MICCAI and is a member of the editorial board of the Medical Image Analysis journal. Menze studied physics in Heidelberg (Germany) and Uppsala (Sweden) and obtained a Ph.D. in computer science from Heidelberg University in 2007.

Dmitrienko recently spoke at the ambitious 'Digital Future' event in Berlin, hosted by the Hasso Plattner Institute and the capital newspaper Tagesspiegel, among others, about blockchains and particularly about the much discussed new exchange medium Bitcoin. The public mostly regards this as highly speculative and risky, but the professor sees Bitcoin's potential to provide more transparency and to question economic or political elites. When asked if she sees Bitcoin as a pure object of speculation, Dmitrienko said: 'I believe that a high fraction of value of Bitcoin, but not all of it, is driven by speculation. The fraction of speculative transactions will go down, and after some time we will see its real value, driven by use as a payment instrument and in commerce.'

However, the expert takes a critical view of blockchain technology in relation to the healthcare system. 'In my opinion,' she explained, 'the application of blockchains for healthcare services is not straightforward, since privacy of health records is a strong requirement, which cannot be easily fulfilled. Only when this problem is solved, could one expect all the innovation potential of blockchains being available to this application domain.'

The professor sees Bitcoins already established at various points and as a solution for difficult social issues: 'Bitcoin and other cryptocurrencies can help further decentralise economic power of any single fiat currency. For instance, Caribbean nations started to support cryptocurrency payments, since the lack of banks hinders their tourism business. Here we have a clear niche for crypto payments, and as long as it exists, Bitcoin will have real value. However, I do not think cryptocurrency will be comparable to dollar, euro or pound – at least not in the future.'

Clinical data must be closely evaluated

The amount of clinical image data is immense: according to a figure published by the European Commission in 2011, clinical image data account for 60 percent of all image data collected in the world – in the meantime, according to Professor Bjoern Menze, the proportion is likely to have increased even further.

When asked whether this data is already securely stored to benefit patients, Menze said: 'Safety is important, but overemphasised! On the contrary, good systems should be brought together to address epidemiological issues. Many studies today could only be carried out with immense effort. With the right algorithms, CT images could reveal much more information than before – for example, random findings.'

The problem is transferring the algorithms to the hospital – into the treatment room. The question is about money and demand and, last but not least, how the infrastructure in hospitals is structured. However, Menze sees a change in the attitude of industrial suppliers. Unlike five years ago, major players, such as Siemens or GE, are relying on interoperability and have understood that the future lies in flexible solutions that are developing with the openness of physicians to new evaluation methods.

Menze is clear about the electronic health card (eHC), which he considers a failure. However, this would not lead to the idea of abandoning data collection in the interest of patients; on the contrary, Menze sees the opportunity to collect information in smaller units. The problem with the eHC, for example, was that it was thought throughout Germany that data collection could be approached more successfully if, for example, one thought within a federal state or within a large hospital chain.

Menze sees Israel as a positive example, where image information and diagnostic reports are standardised within the framework of contracts with hospitals. Much of the information is stored on servers.

Structured data management is therefore not Utopia, but common practice in many places.

Alexandra Dmitrienko is currently Head of Secure Software Systems Research Group in the Department of Computer Science at the University of Würzburg. The internationally sought-after lecturer studied at Saint-Petersburg State Polytechnic University in Russia from 2001 to 2005 in the Bachelor's programme. Dmitrienko's current research interests include blockchains.

ation gains award

epidural complication

pain by avoiding postdural puncture headache (PDPH), a common complication of epidural anaesthesia. PDPH occurs when the anaesthesiologist punctures the dura mater, an act that can generate a breach through which spinal fluid escapes.

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gineers to develop a sealing system to help avoid thcare and biomedical R&D in Spain, Garcia was in the European Under 35 Innovators 2017 program

This app will become as normal as having a camera

Smartphone to measure light spectrum

Report: Madeleine van de Wouw

Checking a lump for malignancy, finding out if food is fresh, just with your smartphone? It's possible, according to Eindhoven University of Technology researchers in the Netherlands.

Their recently presented spectrometer is small enough to insert into a smartphone. This device is not yet ready for use on a big scale, Professor Andrea Fiore, supervisor of the Eindhoven research team points out.

Spectrometry is the analysis of visible and invisible light. Every material and tissue has its own spectrum of light absorption and reflection. Some information on the spectrum of visible light is already gathered by our eyes – it gives the colour of the material. The invisible part of the spectrum also carries a lot of useful information, and can be 'seen' by a spectrometer.

However, current devices are large due to the work they need to do: splitting light into frequencies (different colours). Each frequency must be measured separately, which can only be made some tens of centimetres after the splitting.

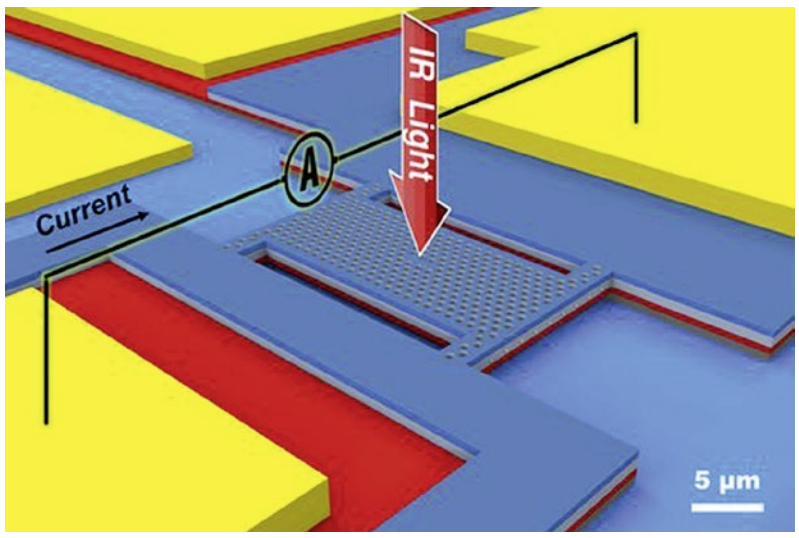
Small v. big

Created by Zarko Zobenica, a PhD candidate at Eindhoven under the supervision of Professor Fiore and colleague Dr Rob van der Heijden, the new microscale device is a small version of normal tabletop spectrometers currently used in scientific labs. The difference is the way the small spectrometer works.

The researchers developed a sensor that uses a photonic crystal cavity, a 'trap' of just a few micrometers into which incoming light falls if it has the right frequency. Fiore: 'This trap is contained in a membrane, into which the captured light generates a tiny electrical current that is precisely measured, retaining just a very tiny frequency interval and therefore measuring only light at that frequency.'

Two of the membranes were placed closely, one above the other, allowing them to influence one another: a slight change in distance means the measured light frequency also changes. To ensure a varying distance between the membranes, the researchers incorporated a MEMS (micro-electromechanical system). A similar type of MEMS is already present in smartphones and other devices to sense free fall and put the sensitive parts in secure mode before ground impact.

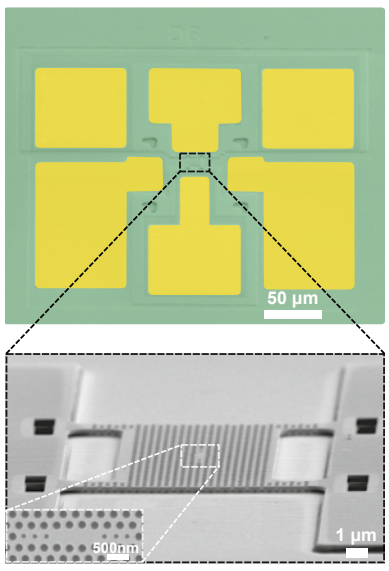
Sketch of proposed microspectrometer



Fiore: 'Using our present system, the sensor covers a wavelength range of around thirty nanometers, within which the spectrometer can discern some hundred thousand frequencies. This is exceptionally precise because we can control distance between the membranes to just a few tens of femtometers' (one femtometer is one millionth of a billionth of a meter, or about one million times smaller than typical atom size).

Applications

Measuring light gives a spectrometer a wide range of applications – two of the most interesting being in food and medical industries, says Fiore, used, for example, to measure CO2, check the pill you take is correct, measure blood sugar level via thin skin on the earlobes. Another application is to gain skin and tissue information, for example during surgery, using the spectrometer to determine whether exposed tissue is cancerous and help decide how much tissue to be removed, he suggests.



Above: Optical-microscope image of fabricated microspectrometer
Below: Electron-microscope image of the active area, with zoom-in on the photonic crystal cavity

The frequency range is too small to use on a big scale, Fiore explains. 'The sensor covers only a few percent of visible and near-infrared light, the most used part of the spectrum. We need to expand this range for more general use. We also will need to integrate a light source so that the smartphone sensor can function independent of external sources. So, it will take years before the new spectrometer will be integrated within a smartphone and at least ten years before it's on the market.'

The future

Many companies and scientists are developing microspectometers, with different approaches. The Eindhoven team is also working to enlarge the measured spectrum width. 'The technology will get there,' Fiore assures. 'The question is only whether a market for these microspectrometers exists and, if so, which company will produce them. If I'm correct, the future will show that having a spectrometer in your smartphone is as normal as having a camera. The only thing is the future must wait a couple of years.'

Prof Andrea Fiore graduated in Electrical Engineering and Physics from the University of Rome 'La Sapienza'. Between 1994-97, he wrote his PhD thesis on nonlinear frequency conversion in semiconductor waveguides at Thomson CSF Central Research Laboratory (Orsay, France). He held postdoctoral appointments at University of California in Santa Barbara, at the Ecole Polytechnique Fédérale de Lausanne in France and a research position at the Italian National Research Council. Between 2002-07, as assistant professor he led Quantum Devices activities at the Ecole Polytechnique Fédérale de Lausanne. Since October 2007, he has been Chair of Nanophotonics at Eindhoven University of Technology, the Netherlands.

Tackling an epidural anaesthesia complication

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Being able to seal this breach by placing an implant can help prevent the occurrence of invalidating and sometimes long lasting headaches, according to Carlos García Vitoria, an anaesthesiologist from Valencia, who long thought about a way to get past the problem.

'Epidural puncture aims to relieve pain, but paradoxically in 2% of cases it can cause a more intense and lasting pain than the original discomfort, which motivated drug administration. We need to evaluate how to act before headache occurrence to discard this invalidating clinical scenario,' said García, who led a team of anaesthesiologists and engineers from Dr Preset University Hospital and Valencia Biomechanical Institute to develop Duralock, a sealing system that can help avoid PDPH.

The system comes in a kit that includes an implant and tools necessary for its insertion through a needle that is conventionally used in epidural puncture. The implant can be applied in 30 seconds with just one hand in a completely sterile way, and does not present any risk of additional dural perforation, García pointed out.

Besides impairing the patient's life, PDPH can extend hospital stay by five days and generate higher healthcare costs. In 2005 in Spain, accidents occurred during 3,425 dural punctures. García estimated that Duralock could help to save as much as €10,500,000 annually for the nation's health service.

The team's solution, named Duralock, comes in a kit that includes an implant and necessary tools for insertion through a needle

Due to the award, received in March in Madrid, the product can benefit from the medical industry's expertise to help speed up release to market, notably by helping recipients to remodel strategy and business plans. Among the winning initiatives, Duralock will be featured at BioBoston 2018 and JP Morgan Healthcare 2019 in San Francisco, to boost its visibility in the North American market.

Nothing gives

Doctors working in the eight-bed Paediatric Intensive Care Unit (PICU) at the Ramón y Cajal University Hospital in Madrid extensively use point-of-care ultrasound to evaluate the condition of critically ill children, and they find it essential in their work, as Dr José Luis Vázquez Martínez, Head of PICU at Hospital Ramón y Cajal, with over 25 years' experience in paediatric intensive care medicine, explained.

Point-of-care ultrasound (POCUS) is used extensively in our unit, allowing comprehensive, head-to-toe assessment of critically ill children, including respiratory, oncology and post-operative cardiac patients, as well as those being treated for sepsis or multiple trauma. The POCUS approach allows not only an initial diagnosis, but also routine monitoring of treatment to see whether or not a patient's condition changes, enabling alternative strategies to be implemented if there is no improvement.

POCUS helps paediatric doctors in many ways. For example, ultrasound scans enable evaluation of a patient's haemodynamic state, looking at their heart function and blood volume to see if these factors are contributing to respiratory failure. Conversely, doctors can see if a lung problem, such as pneumonia, is affecting the heart. For a patient in a coma due to multiple trauma, ultrasound is used to look for signs of bleeding – a potential cause of unexplained anaemia – and to assess the intracranial pressure.

It's also used to monitor kidney function in children with blood pressure problems, and visualise intestinal indications of sepsis. In addition, ultrasound guidance can be used for endotracheal intubation. In short, broader applications that we did not anticipate until very recently.

We have used ultrasound in our PICU for more than a decade, and have always had SonoSite systems, upgrading them as new technology is introduced. In the beginning, when my knowledge was more limited, the aim was to perform clinical echocardiography but, when the SonoSite representative showed me the linear probe and the various

15th century hospital shows tomorrow's health 'cells'

Designer visions for future hospitals

Report: Carla Zimmermann

In the hustle and bustle of the Salone del Mobile – Milan's famous design week – an oasis of peace and calm comes as a surprise. The Cortile dei Bagni is such a surprise; this inner bath courtyard is part of a Milan hospital built in the 15th century. Here, architect Filippo Taidelli installed a contemplative space experience that tells a story about the future of healthcare. Its title 'Cells' refers not only to the cells of the human body but also to the word's Latin origin: cella, small room.

In two cells at opposite corners of the courtyard visitors can explore two opposing tendencies of modern healthcare: the first room visualises technology-oriented medicine which creates a virtual healthcare environment for the patient, redefining the relationship between humans and technology. In the second room the interior of a hospital is shown that increasingly tries to emulate a 'home'.

Sci-fi atmosphere

The first cell is mirrored; the interior is invisible from the outside. From inside, however, there is a clear, unobstructed view of the outside. In the world of healthcare this paradoxically creates an initial sense of comfort and shelter. The 2x5x3 metre cubicle embodies the future relationship between human beings and healthcare technology, a relationship many people expect to be dominated by technology; to be virtual and sterile.

The atmosphere is reminiscent of a science fiction movie, complete with a sound dialogue between a human being and an avatar filling the sparsely furnished room. The ceiling window pretends to open up to the sky – but it is virtual sunlight, produced by a company called Coelux to create the effect of natural light in hospitals. The moment visitors become aware of the virtuality of the space – and the sensory experience will produce this awareness – the sense of comfort vanishes and a feeling of being locked in creeps up.

The more virtual healthcare becomes, the less sensory it will be. No doubt, the senses can be simulated by technological means, but how do patients feel when their recuperation depends on an interaction with avatars?

Peace and wellbeing

The second cubicle, located at the other end of the courtyard, represents the architectural future of hospitals and their impact on a patient's environment. The cell's transparent outer shell symbolises the link to nature, which will play an increasingly important role in healthcare. There are pleasant smells, warm light and ambient music, sounds of nature interspersed with children's laughter. Created by designer Nicola Ratti, this sound world envelopes the patient in a comfort blanket.

The furniture is friendly and unobtrusive. The table and interior floors, by Casalgrande Padana, are made of porcelain. Their antimicrobial properties were achieved by a special treatment of the surface.

Contemporary hospital interior design welcomes nature in order to tap into nature's healing powers: muted colours, pleasant sounds and smells create an oasis of peace in an increasingly chaotic world – a place that provides shelter to the ill. The transparent space, which asserts the need of sensory wellbeing does, however, link up with a virtual world of healthcare: the transparent walls provoke reflections on privacy, a further important aspect of future healthcare.

The installation is a joint project by architect Filippo Tadelli, Raffaello Furlan, professor of internal medicine at Humanitas University in Milano, and Dr Mauro Gatti, Research & Business at IBM Italy, all with previous experience in healthcare and technology concepts.

The cells were produced by Universal Selecta, a Milan-based interior design company that specialises in creating sound-absorbing spaces.

This impressive installation, with its spaces reflecting on the future of healthcare, raises the question of how today's healthcare system can move towards a better future… how it can achieve a balance between virtuality and sheltering the patient. This could be the time for more hospitals to integrate design trends to support healing by providing a positive sensory environment.

Above: The installation, which ventures into the future of healthcare, is located in the courtyard of the old Milano hospital.

Below left: A mirrored cubicle represents the future relationship between humans and technology.

Below right: A second cubicle represents the architectural future of hospitals and their impact on patients' environment

Like a ventilator, ultrasound is essential in an ICU

s so much info so quickly

techniques available, it was as if I was being shown electricity after using candles! It was amazing, a real turning point in the use of ultrasound, and everyone recognised it as a step forward in the paediatric intensive care world.

Dr. José Luis Vázquez Martinez, Head of PICU at Hospital Ramón y Cajal, is a pioneer in using ultrasound across Spain

For the patients, a major benefit of ultrasound is that exposure to radiation can be reduced. Before ultrasound, X-ray examinations were performed two or three times in the first few days after admission to try to establish the cause of the problem, often with limited success. With ultrasound, we can scan the patient as often as necessary, implementing treatment and monitoring its effect without exposing the child to more radiation.

In PICU, we consider an ultrasound system essential – there is nothing else that gives us so much information, so quickly and non-invasively – and today we have a dedicated Edge II ultrasound system with linear, including hockey stick, and adult and paediatric cardiac transducers. It is in constant demand and is a perfect fit for our work, fulfilling all our expectations. All my colleagues use it, and we are very satisfied with it.

The system is high quality and ergonomic, and strikes a good balance between image quality and ease of use. It is also quick to boot up, which is crucial for an instrument that is frequently moved between different beds in the unit. Robustness is vital too; if a patient deteriorates, we may have to move any equipment surrounding the bed very quickly to create space to treat them. However careful you are, there is always the risk of unintentional knocks to the system.

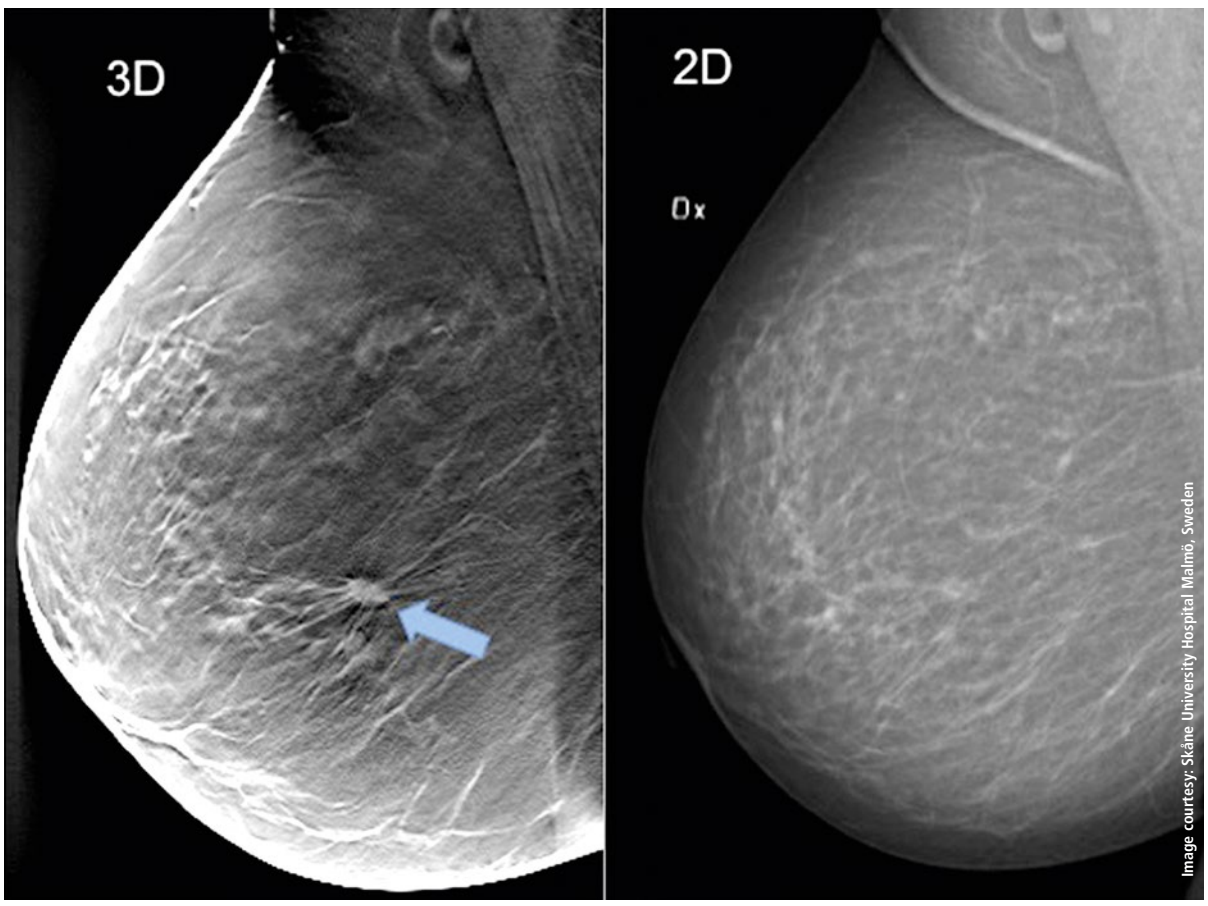
A while ago someone said to me that they 'sell ultrasound machines, but don't offer training', but this view isn't enough – it's very short-sighted – training is very important. Ramón y Cajal pioneered the use of ultrasound in PICUs across Spain, and was the first hospital to offer external training courses for doctors from other facilities, initially focused on clinical echocardiography. Over time, this has expanded to include neuromonitoring, respiratory and abdominal monitoring. I acquired my ultrasound experience through a combination of external training in adult ultrasound and practical, hands-on learning, and am largely self-taught. If courses like these had been available when I started using ultrasound, I would have saved so much time. FUJIFILM SonoSite is clearly committed to organising and supporting ultrasound training, and this is unquestionably a great benefit to the scientific community – long may it last!

Today, we are seeing a boom in the use of ultrasound in paediatric care, as it non-invasively provides immediate information in situations where time is of the essence. Our advice to people attending our training courses, who do not have – or have to share – an ultrasound system, is to tell their hospital managers that, just like a ventilator, it is an essential piece of equipment for an intensive care unit.

Digital breast tomosynthesis improves diagnosis

DBT could boost breast screening

Tomosynthesis is under international review, with a surprising number of enticing studies carried out in Northern European countries, among them one headed by Professor Sophia Zackrisson at Lund University, Sweden. When interviewed by Lena Petzold of European Hospital, she not only revealed surprising trial results, but also shared her thoughts on practical implementation and unusual speed-reading methods.



3-D mammography (tomosynthesis) to the left shows a 1 cm large tumour which is not as clearly visible on the 2-D mammography image to the right. The breast is quite fatty and it is evident that not much overlapping tissue is needed to compromise lesion visibility on 2-D mammography and hence the case illustrates the superiority of the tomosynthesis technique.

'Our institute's connection to tomosynthesis goes a long way back,' explained Sophia Zackrisson, senior consultant radiologist at Skåne University Hospital. 'We began to try out a prototype unit from Siemens as early as 2006 under my mentor Ingvar Andersson, a well-known breast radiologist and researcher. We were, and still are, positively surprised by the technology's benefits, especially in terms of eliminating the so-called overlapping tissue effect.

'We were quite sure that tomosynthesis could have a major impact on screening, so we started some initial smaller studies. Yet, to really prove its effects, we needed data on a much larger scale, so we set out to implement a prospective trial.

'When we decided on the basic outline, we reviewed the principles of screening: it should be acceptable for the population, should be fast, and should be safe. So, we decided to use a very simple protocol and show that it is still feasible to gain the same or even better results with one-view digital breast tomosynthesis (DBT) than two-view DBT + digital mammography (acquired or synthetic) as compared with two-view digital mammography (DM). We used the Siemens Mammomat Inspiration, but actually read the images on our regular Sectra PACS system.

'We screened nearly 15,000 women over several years. Our participants were recruited from the regular screening population in Malmö, where according to Swedish recommendation every woman between 40 and 74 years of age is invited in different intervals for a preventive screening. Participants received the regular two-view mammogram first and then were screened with one-view DBT and reduced compression, a special feature of the trial.'

Results

'We collected a huge amount of data; and our most important results were that we not only found more predominantly invasive cancers in all density categories but that the detection rate with one-view DBT was 34 percent higher than with DM. When starting out, we were hoping for a 10 or maybe even 15 percent increase, so we were very happy when the results showed such a powerful augmentation.

'We were also astonished that the detection was better in all densities including quite fatty breasts and not just in dense breasts. It shows that you do not need much overlapping tissue to hide a spiculated tumour. Furthermore, we were happy that we could reduce the compression in the DBT part of the trial by up to forty percent without losing valuable image quality. This could positively affect future screening attendance rates, since many women refrain from going because they fear the painful part of the examination.

Dose

'Another positive effect we came across concerned the radiation dose. We were able to use a 15 percent lower so-called average glandular dose for one-view DBT than two-view DM. Though radiation exposure has lost much of its significance in discussions, since we could strongly reduce dosage over recent years, it is still a valuable accomplishment if we can improve our results and lower radiation exposure at the same time.

How can DBT image reading time be decreased?

'If I had an answer to that, I'd probably be rich. It's a difficult question with no clear-cut solution. However, there are several promising studies and approaches. One way to shorten reading time could be to use the so-called slabbing technique, where thinner image slices are combined in thicker slices to reduce the image volume.

'Hotly discussed are also developments including AI and Deep Learning. I myself would like to navigate easier in the tomo-stack, so a CAD system that indicates important features or lesions would be much appreciated. I could also imagine a system trained on a big data set that gives you a rating of probability of malignancy to be beneficial. So CAD and AI are very likely the way forward to assist radiologists finding the relevant parts in the DBT volume more quickly.

'Another interesting experiment was conducted recently: Our research group used an eye tracker to see how fast readers were finding lesions in differently presented DBT images, and found out that, when DBT images were displayed horizontally, the radiologists read them a lot faster, because their eyes were more adjusted to the horizontal alignment.

'There is powerful potential for improvements out there, but we also should not forget that reading images has always been a matter of training and experience. It's not unthinkable that we can reduce time and improve sensitivity and specificity significantly simply by working with DBT on an every-day basis. It has almost become a proverb by now, but we really need more studies in this area.'

Future plans

'There's still a lot of information to analyse from the trial, such as biological tumour characteristics. But, we are also planning to execute a meta-analysis of three studies in the first step – the STORM, Oslo and Malmo trials – including even more trials along the way to get influential results and see if we can show, for example, a common decrease in interval cancers.

'The question that always comes up is: are we going to implement tomosynthesis in screening? Ultimately, I don't know, but I am positive that it could happen. Breast cancer screening is one of the best screening programs we have in Sweden, but DBT could enhance it even more. It will be a long journey, but I'm convinced that, if you want to improve, tomosynthesis is an easy way forward. You just replace a unit in the same building in the same room with the same technologies and receive better mammography. People only need to be convinced of the benefits.

'If you start using DBT in your own practice, you soon notice how many cancers you miss with 2-D only and usually that's enough to convince people. Tomosynthesis is not perfect and we should not have blind faith in it, but it's a great screening tool for a vast majority of average risk women. Personally, I think that a grass roots approach would help.

'Start in several places by installing units in different centres and invite radiologists to try them out. When using it yourself, you really understand what the technology can give.'

Associate Professor **Sophia Zackrisson MD PhD** is senior consultant radiologist at Skåne University Hospital in Malmö, Sweden, and a senior lecturer in radiology at Lund University and research group leader of diagnostic radiology. Her research focus lies on mammography screening and breast cancer. She received her medical degree from Lund University in 1999 and her PhD in Epidemiology in 2006. Following her residency in radiology in Skåne, from 2012-17 she headed the department of oncological imaging at Skåne University Hospital.

Like a box

Machine learning

Standardised and well-structured data, as well as the definition of clear objectives, are indispensable prerequisites for artificial intelligence implementation into clinical processes.

Report: Michael Krassnitzer

'Ask not what artificial intelligence can do for you but what you can do for artificial intelligence!' This variation on John F Kennedy's famous quote comes from Dr Ben Glocker, Senior Lecturer in Medical Image Computing at Imperial College London, UK. The occasion was a lecture given by the computer scientist at the European Radiology Congress (ECR 2018) on how machine learning can be routinely implemented in medical image analysis.

Artificial Intelligence (AI) was among the main topics at the congress; this also includes machine learning and its subdivision 'deep learning', which is based on so-called neural networks. AI entails an artificial network learning from examples and recognising inherent patterns and regularities by itself. Based on this, numerous applications are already used in imaging, such as image segmentation, where an algorithm precisely marks out certain anatomic or pathological structures from their environment (e.g. healthy brain tissue from tumour tissue in MRI brain scans, or whole body MRI scans of organs). Machine learning also facilitates the detection of new disease patterns, the extraction of clinically relevant information from multi-dimensional, multimodal image data that would otherwise remain concealed.

Clearly defined objective needed

'It's basically a mathematical function,' says Glocker explaining machine learning. 'This function is fairly complex, and we also cannot say exactly what is looks like, but like every function it has an input and an output.' According to this UK-based German computer scientist, there are frequently misleading ideas around the necessary input.

Women should know about breast density

Driving cancer screening compliance

Formalising protocols can lead to better patient outcomes, advises Tracy Accardi, Hologic's Global Vice President of Research and Development for Breast Health & Skeletal Solutions

Breast density: it's a topic that comes up often in the breast imaging industry and plays a crucial role in breast screening, as women with very dense breasts are four to five times more likely to develop breast cancer than women with less dense breasts (1. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. N Engl J Med. 356(3):227-36, 2007. 2. Yaghjyan L, Colditz GA, Collins LC, et al. Mammographic breast density and subsequent risk of breast cancer in postmenopausal women according to tumour characteristics. J Natl Cancer Inst. 103(15):1179-89, 2011.).

Additionally, the masking effect that breast density can have on an image, which can make it extremely challenging for radiologists to see and diagnose cancer using traditional 2-D mammography, demonstrates that breast density greatly impacts on the breast screening process as a whole. These facts make it particularly important for radiologists to educate their patients about what their breast density is and what that means for their health.

According to a 2017 Kadence study, 74 percent of radiologists surveyed in Europe talk to their patients about dense breasts and, of those, 25 percent list diagnosis/detection as their top challenge when it comes to screening women with dense breasts. However, only two percent of the surveyed radiologists have a formal screening protocol in place for patients with dense breasts (Kadence study conducted in partnership with Hologic in 2017. Data on file.).

The proven impact of density on screening, coupled with these research findings, shows a clear need for radiologists to formalise their approaches to addressing breast density, from patient education and assessment through screening. This will help to ensure that all patients – including those with dense breasts – have the best possible clinical outcomes.

Driving breast cancer screening compliance is an essential part of improving clinical outcomes, and one way to do this is to educate women about their breast density. Knowing breast cancer risk factors, such as family history, can help encourage patients to remain compliant with screening guidelines, and breast density is no exception. By informing patients who have very dense breasts that they may be at greater risk for breast cancer diagnosis, radiologists can help improve screening compliance among women who may not have previously felt a strong need to be screened. Therefore they may have a better chance of early cancer detection. However, to be effective, discussing breast density with patients starts with breast density assessment, an exercise that is currently undergoing a great deal of change, especially as artificial intelligence (AI) continues to advance.

Typically, to categorise their patients' breast density, radiologists complete a visual assessment of digital images using the Breast Imaging Reporting and Data System (BI-RADS) classification established by the American College of Radiology (ACR) in 1993. The current need for a visual assessment to indicate a BI-RADS score means that breast density categorisation can be subjective to the person reading the images and lead to variations depending on who is looking at the image. The rising trend of machine learning in the medical device space, however, is becoming increasingly relevant specifically for analysing breast density. Machine learning-based algorithms are especially useful for classification issues, and categorising breast density using parenchymal patterns and texture is just the type of need these algorithms can help fulfil.


S Ciardullo (https://commons.wikimedia.org/wiki/File:Mamas_Densas_1_CC.JPG), „Mamas Densas 1 CC", https://creativecommons.org/licenses/by-sa/3.0/legalcode

When combined with expertise from radiologists, who can provide patient and situational-specific context to supplement the AI, the use of such technology can help standardise breast density classifications. Thus, machine learning can greatly impact on breast density assessments by providing a more uniform, objective classification system across the industry. Thus clinicians can make more confident screening decisions and recommendations for their patients.

Since dense breast tissue can make identifying cancers more difficult on certain imaging modalities, breast density can help to inform which screening protocol is best for each patient. This can vary based on the pros and cons of the technology and specific needs of a patient. Ultrasound, commonly used in Europe for example, is very useful for women with dense breasts because it can identify the difference in density between tumours and the breast tissue around them. Unfortunately, ultrasound also has significantly higher false positive rates. Contrast enhanced breast MRI provides very clear images that make it easier to spot cancer in dense breasts and doesn't use ionising radiation, but it can also lead to false-positives, is very expensive and is limited in availability.

Although 3-D digital mammography uses a radiation dose, it provides accurate, high-quality images that can help detect invasive cancers – and it is without question that accuracy is by far the most important part of any breast screening. If a radiologist was to perform a 3-D mammography exam on a patient with dense breasts and not see anything, then he/she can be especially confident the patient is done with screening and only move on to an ultrasound option if there are any suspicious spots.

Despite the fact that there is no general consensus on what screening protocols for dense breasts should be, some imaging modalities are more effective than others. In fact, Hologic's 3-D Mammography exam is the only mammogram that is FDA-approved as superior to standard 2-D mammography for routine breast cancer screening of all women, including those with dense breasts (FDA submissions P080003, P080003/S001, P080003/S004, P080003/S005.). Therefore, radiologists should place more of a priority on formalising their breast exams based on breast density, while of course keeping in mind any other relevant factors distinctive to each patient.

The concept of breast density is an eye-opening one because it truly captures the unique profile of each patient. Although two women may have the same breast density classification, other factors in their life, such as family history, race and more, each play a different role in creating a somewhat different patient profile. By addressing breast density head-on through educating patients on the topic and implementing a more formal assessment and screening process, radiologists can help each patient have the best chance of early cancer detection, which is the ultimate goal for all.

Tracy Accardi MSc is Hologic's Vice President of Global Research and Development at the Breast and Skeletal Health Division.

of pumpkins, data contains big variations


Source: Pixarbay / birgl

Expectation v. reality: Like variously shaped pumpkins, radiology data sets can differ significantly from one another

'The approach "We have a lot of data and are going to do something with it with the help of machine learning" is not the best starting point.' Therefore, Glocker's first advice is: If you want to use machine learning successfully you need to start with a clearly defined objective. 'Machine learning is always geared towards a very specific task,' he emphasises.

Another common obstacle to the use of machine learning is the quality of data. Glocker explains that, on many occasions, clinicians promise him homogenous data sets for respective projects, which actually turn out to be different, insufficiently structured data. He compares this to pumpkins: 'We are expecting a box of these vegetables of equal size, equal shape and equal colour, but what we actually receive is a delivery of pumpkins of different sizes and different varieties.' For data to be used for machine learning it not only needs to be correct and labelled but most definitely also standardised and labelled in a standardised way.

'Machine learning can only begin when data is usable and when a specific task has been determined,' Glocker concludes. The development of an AI application also needs the relevant medical expertise for its use: 'The experts must be involved in all stages of development,' the computer scientist emphasises. He means that medics and computer scientists must work together in interdisciplinary teams. He also offers other inevitably important advice: 'Artificial Intelligence applications must be integrated seamlessly into clinical processes.'

Ben Glocker PhD is a senior lecturer in medical image computing at Imperial College London, UK, and deputy head of its biomedical image analysis group. He gained his PhD from the Technical University Munich, Germany. He was then a post-doc at Microsoft Research and a research fellow at the University of Cambridge, United Kingdom. In his research he specialises on applying machine learning and artificial intelligence to automate image analysis.

Machine learning: a valuable radiologists' assistant

AI will make them data scientists

Machine learning is increasingly helping radiologists to acquire faster and better quality images, and measure heart function. This is just the tip of the iceberg; artificial intelligence has far more to bring to the heart, explained Daniel Rueckert, Head of the Department of Computing at Imperial College London, during CMR 2018.

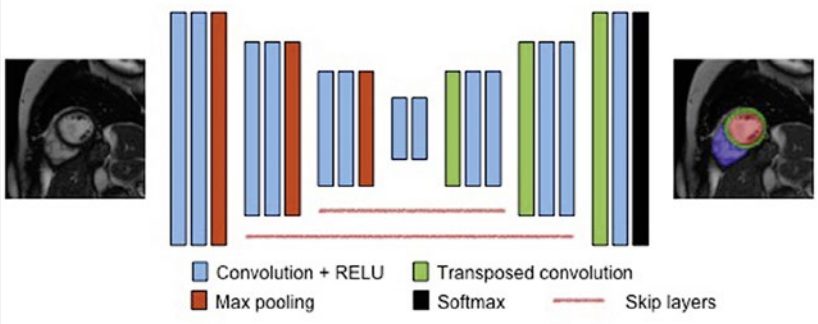
Report: Mélisande Rouger

Machine learning (ML) is becoming a valuable assistant for radiologists performing cardiovascular MRI. ML tools mainly help clinicians to acquire better images of the heart in shorter episodes of time, a key factor that can improve examination quality and increase patient comfort, according to Rueckert. 'Typically, patients need to hold their breath several times while the examination is being performed. The sicker you are, the more complicated it is to hold your breath, and this may impact examination outcome. So here the machine simply helps you get the images faster and in a more comfortable way,' he said.

ML also enables functional parameters measurement, for instance of how much blood the heart can pump per heartbeat. To do that, radiologists typically measure the heart when fully relaxed and when contracted. The difference indicates how much blood the heart can pump.

The operation requires labelling every pixel in the image depending on which part of the heart is being observed, so one can actually compute that measure; but with machine learning, this can now be done automatically, Rueckert said. 'You can effectively analyse the images and automatically perform segmentation. Then you show the clinician what segmentation looks like, and if they're happy, they can accept that and get these measures automatically.'

Convolutional Neural Networks for Image Segmentation



© Bai et al.

For the moment, machine learning use is limited to assisting the radiologist in doing 'basic' tasks. But this is just the bottom of the pyramid, said Rueckert, who used the reference to illustrate the machine's contribution to medical imaging. 'In the future ML may well help the radiologist to perform high-end tasks, for instance directly diagnose disease from an image. Research is underway in this field and applications are emerging, but it may be a while before they effectively serve the radiologist,' he said.

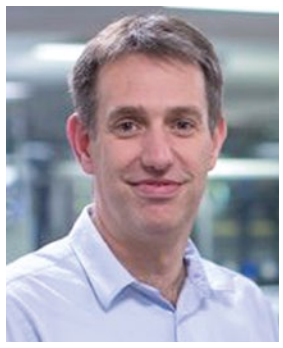
The solutions developed so far will not replace radiologists, but rather make things easier for them at work, he added. 'A lot of what has been developed in recent years are techniques that would make working easier for the radiologist, but are not designed to replace the radiologist.'

Rueckert's comments followed debates about radiologists potentially losing their jobs to ML and other artificial intelligence-based solutions. This, Rueckert is sure, will definitely not happen. 'ML is a tool which radiologists will all use in the future when they look at images, and it will help to make better decisions based on better images. But I repeat, it will not replace them,' he said. Artificial intelligence has the potential to boost the radiologist's contribution and value in the chain of healthcare – for example by bringing in quantitative assessment to the radiologist's report, an objective information that is currently missing. 'When radiologists look at the image and then make a report, they give you a very qualitative assessment of what they have seen. A blood test will give you a reading value, a quantitative measure, but an imaging examination won't give you that for the moment. I think we will see much more quantitative radiology. The report will give you a number and that number might be a criteria of information, Rueckert suggested.

This will help establish the probability for a diagnosis, and may help clinicians to diagnose earlier and more confidently. Quantitative measures may also help identify further conditions, which often go unnoticed when screening for a particular disease, Rueckert added.

'One thing that is quite overlooked is that it's quite common for people to have a multitude of diseases; you often have a mix of things. Taking in a probability for a certain disease may be the right thing to do, because it can reflect that you have certain other diseases,' he said.

A myriad of potential applications could benefit from ML, not only risk identification and disease prediction, but also treatment guidance. 'If you want to perform heart surgery you need imaging to guide you; so, ML could help use imaging more appropriately in this setting as well,' he explained.



Professor Daniel Rueckert heads the department of computing at Imperial College London, which he joined as a lecturer in 1999 and became senior lecturer there in 2003. He has been professor of visual information processing and led the biomedical image analysis group since 2005.

Machines may not threaten radiologists, but their jobs will be transformed. 'ML will probably make life a little bit more complicated for radiologists, who in the future may become something more like data scientists – people who need to interpret a lot of information from different sources, from imaging and maybe from non-imaging examinations – genetics tests for instance. So, their work might become more complicated, but technology will support them in that change.'

Radiologists will need proper training to be able to use these tools, communicate with computer scientists and understand when to and not to trust the machine.

'Clinicians need to understand what is being said and to know what they can rely on; when should they trust the machine and when it is just an opinion. The machine cannot give you a definite answer but it can help in case of doubts.'

AI will not replace radiologists

Intelligence: augmented rather than artificial

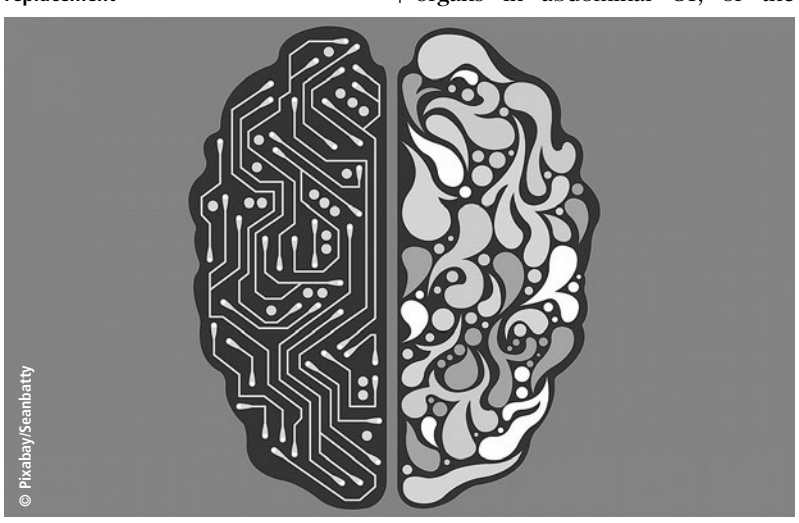
Artificial intelligence (AI) will increase efficiency and improve quality as well as clinical outcomes – and thus strengthen rather than weaken the role of radiologists, said Dr Joon Beom Seo at ECR 2018, as EH correspondent Michael Krassnitzer reports.

A spectre is haunting radiologists – the spectre of artificial intelligence. Is AI about to replace radiologists? Wrong question,' declared radiologist Dr Joon Beom Seo, professor at the Artificial Intelligence for Medical Imaging Research & Development Centre, University of Ulsan in Seoul, South Korea, during his presentation at ECR 2018. He responded with an alternative question: 'How can we improve and reposition radiology by integrating AI technologies?'

The term artificial intelligence in the context of radiology usually describes applications based on deep learning: an artificial system learns from examples by autonomously recognising patterns and structures. To date, such applications are already available for all areas of image analysis, be it image conversion and segmentation of lesions and organs or the detection and classification of lesions.

Seo cited some examples of image conversion applications: images acquired with a certain filter can be converted in a way that they seem to have been acquired with a different filter. While in low-dose CT deep learning applications can reduce noise; in Diffusion Tensor Imaging (DTI) they can increase image quality such as spatial resolution from 2.5 mm to 1.25 mm and the number of gradients from 15 to 90. 'Image conversion using deep learning methods is a promising area,' Seo pointed out, because it might, inter alia, solve the issue of heterogeneous data in multi-centre studies.

AI is a tool for the radiologist, not a role replacement



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More automation = less time, less effort

'AI-assisted segmentation of lesions and organs can already be carried out in a fully automatic way,' the South Korean expert suggested. For example, the segmentation of organs in abdominal CT, or the detailed visualisation of the respiratory tract in thoracic CT. 'Deep learning methods display the organs as well as manual post-processing. However, the computer will do in two minutes what the radiologist does in two hours.' Thus, AI offers a significant reduction in time and effort. 'Introducing this technology into clinical routine will be the dawn of a new era,' Seo said, with enthusiasm.

The same, he believes, holds true for detection and classification of lesions. AI already delivers great results in the case of CT detection of lung nodules. This could also be introduced to clinical applications, said Seo: the computer might check the scans for suspicious areas and report them for review before the physician looks at the images.

Nevertheless, at this point AI still operates in a rather restrictive environment, Seo emphasised, pointing at political and legal concerns regarding privacy and commercial use, but also at technological issues. Most importantly, however, many radiologists are worried about the fact that deep learning systems are black boxes: 'We do not know how a system arrives at its results,' Seo explained.

Courtesy of Asan Medical Centre Seoul

Joon Beom Seo MD PhD, is professor at the University of Ulsan College of Medicine in Seoul, South Korea, and attending physician in radiology at the Asan Medical Centre in Seoul.

Who teaches the machine?

Currently, AI applications in medical imaging are still based on supervised learning processes, i.e. human specialist input is necessary. This raises the issue of who should or may train the systems. 'If you look for example at the detection of diabetic retinopathy you will see that there are large interobserver differences,' he said. Which goes to show that even a deep learning system depends on the quality of the data it uses to learn.

'Artificial intelligence won't replace radiologists, but rather strengthen their role by improving quality and clinical outcomes and increasing efficiency,' Seo said, returning to the initial question. AI thus is a tool not a replacement of the radiologist: 'We should,' he concluded, 'call it augmented rather than artificial intelligence.'

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CARDIOLOGY 2018

NEWS AND TECHNOLOGY UPDATES FOR CARDIAC CARE

MUNICH • GERMANY 25 AUG – 29 AUG 2018

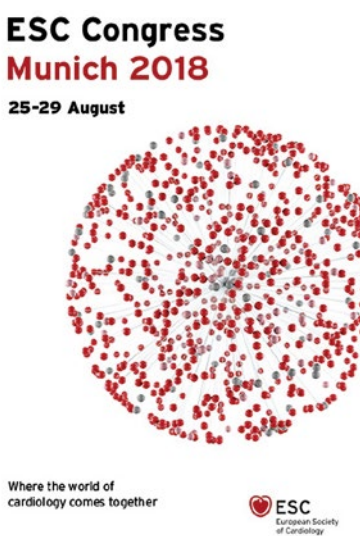
At the heart of research

Scanning impacts on cardiology

When delegates from around 150 countries converge on Munich for ESC Congress 2018 they will no doubt reflect on what they themselves eat. Yes, nutrition is up for debate, questioning, for example, whether weight loss therapies can also prevent heart attacks and strokes. Results from the CAMELLIA-TIMI 61 trial of 12,000 overweight individuals with established cardiovascular disease or diabetes could tell us 'whether becoming slimmer with weight loss therapies also makes you healthier,' explained Professor Stephan Achenbach, Chairperson of the ESC Congress Program Committee and ESC President Elect. That trial is being presented at the congress.

Results with big impact

Additionally, the huge PURE study, which examined what constitutes a healthy diet in over 200,000 people from more than 50 countries, will be aired. 'The results will give us new insights on the relationship between the types of food we eat – for example fruit, vegetables, nuts, dairy products and meat – and health and disease,' Achenbach explained. The Chair also expressed excitement about other trials to be presented, with results 'set to have a big impact, either because they affect large population groups or involve innovative treatments.'



For example, two aspiring trials to examine for preventing first heart attacks and strokes prevention will be presented – the ARRIVE trial involved more than 12,000 individuals at moderate risk and the ASCEND trial involved over 15,000 diabetics. 'We had assumed that taking aspirin can only be good for you, and what's the harm?' said Achenbach. 'But then we discovered that, while aspirin can protect against heart attacks and stroke, it causes bleeding. So it's not at all clear who will actually benefit from taking aspirin to prevent a first heart attack or stroke. These two trials will shed light on this issue, impacting many millions of people worldwide.'

2018 European Society of Cardiology (ESC) and European Society of Hypertension guidelines on hypertension are another important talking point. 'The American guidelines (released in 2017) were very strict and lowered the definition of high blood pressure. It will be exciting to see what the Europeans say about what blood pressure qualifies as "high" and how strictly it should be treated,' Achenbach surmised.

The MARINER trial will reveal whether potentially fatal blood clots can be prevented in acutely ill patients by continuing to administer oral anticoagulation therapy after they return home. 'Treating patients after discharge is a completely new concept and could affect the millions of people hospitalised every year with heart attack, pneumonia, or broken bones,' Achenbach prophesied.

Oral anticoagulation is also a focus of the COMMANDER HF trial, which will reveal whether these drugs improve survival and reduce heart attack and stroke in heart failure (HF) patients who do not have atrial fibrillation. Achenbach: 'This is a massively large patient group that so far not been considered for oral anticoagulation unless they have atrial fibrillation and the trial could change our approach to their management.'

Prof. Jeroen J. Bax, FESC President 2016-2018 of European Society of Cardiology

Trials and more

Achenbach also highlighted the MITRA.fr study, which indicates whether treating the mitral valve with a device inserted via a catheter is advantageous in HF patients.

An entire late breaking science session is devoted to transcatheter aortic valve implantation (TAVI) and is aligned to the congress spotlight, Valvular Heart Disease. This includes the LRT Clinical Trial and GARY registry in low-risk patients, the TAVI-PM study on the durability of TAVI, and the five-year follow-up from the FRANCE-2 Registry, which will report on clinical outcomes and valve durability in high-risk patients.

Major drug trials include ATTR-ACT, which assessed the efficacy and safety of tafamidis in transthyretin amyloid cardiomyopathy, a condition that currently has few treatment options. The High-STEACS trial of more than 47,000 patients will reveal whether using high-sensitivity troponin to confirm the diagnosis in those with suspected heart attack leads to more or less deaths and repeat heart attacks after one year.

'I'm excited by how diverse cardiology is and feel it is my responsibility to represent and balance the needs of the cardiologists, healthcare providers and researchers in every country that belongs to the ESC and also across the entire spectrum of cardiovascular disease,' Achenbach pointed out.

This ethos includes spreading news of scientific findings from ESC journals and registries, guidelines, congresses, and other educational activities.

In our special Cardiology section you will also learn from medical science experts how far machines and scanning skills are shaking the very roots of your discipline.

Enjoy the stimulation of new concepts and technological developments. Enjoy EH along with ESC 2018. Welcome!

Prof. Stephan Achenbach, FESC Chairperson 2016-2018 of ESC Congress Programme Committee

Study examines genes and lifestyle links to dilated cardiomyopathy

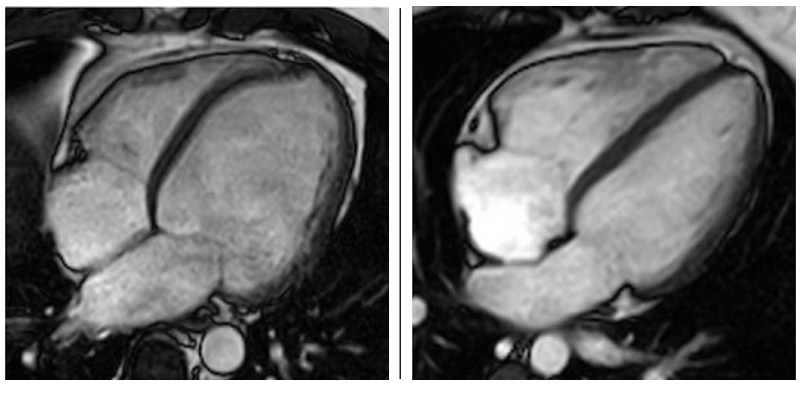
Titin: the commonest genetic cause of DCM

Report: Mark Nicholls

A major study has been launched to investigate the interaction between genes and lifestyle factors and dilated cardiomyopathy (DCM). Led by Professor Stuart Cook, at the National Heart and Lung Institute, this, the largest ever DCM study, will investigate why people develop DCM, with a focus on who is most at risk of sudden death or heart failure (HF).

Six hospital trusts across England – including the Royal Brompton and Harefield NHS Trusts and Imperial College London – will recruit patients for the study.

DCM thins cardiac muscle, making it less able to pump blood around the body. About one in 250 (260,000) people in the UK are affected, with around one in 100 (650,000) believed to be at risk of developing the condition due to a common mutation in the titin protein.



Due to thinned cardiac muscle, a heart affected by dilated cardiomyopathy (left) can pump less blood around the body than a normal heart (right)

This mutation predisposes the heart to developing DCM when it is placed under stress such as during pregnancy, some cancer treatments and possibly alcohol abuse.

Study to improve diagnostics and therapy

DCM is a complex condition and can be caused by a variety of genetic and environmental factors but cardiologists also recognise it is poorly understood, with most causes unknown.

A leading course of heart transplantation, and after coronary heart disease, DCM is the leading cause of heart failure. The condition has poor outcomes with research suggesting that 15% of patients do not survive beyond five years after diagnosis, and up to half of deaths occur within the first two years of diagnosis.

In the new multi-centre study of more than 2,000 patients researchers will use advanced DNA sequencing, biological markers in the blood and cardiac imaging approaches to assess interactions between genes as they seek to discover new genetic mutations underlying DCM, as well as to assess potential environmental interactions.

Ultimately the study aims to find better ways to diagnose, treat and prevent deaths from DCM.

Stuart Cook is Professor of Clinical & Molecular Cardiology at Imperial College London in the UK and head of the Cardiovascular Genetics and Genomics group within Genetics & Imaging at the National Heart and Lung Institute (NHLI). He also directs the genetics and genomics group that plays an integral research role within the Royal Brompton Hospital cardiovascular biomedical research unit. An expert in cardiovascular MRI, with special interest in genetics in cardiac muscle disease, his research focuses on the genetics of cardiovascular disease, particularly inherited cardiac conditions that cause electrical abnormalities of the heart and heart failure.

Professor Cook, who is also Professor of Clinical and Molecular Cardiology at Imperial College

Continued on page 11

Refined guidance with no need for anaesthetic

Intracardiac echocardiography

Intracardiac echocardiography (ICE) is an increasingly important guiding tool for structural heart disease interventions – without general anaesthesia. José Ribeiro, who works in the thorax and circulation unit at Gaia Hospital Centre, Portugal, who has worked with this technology for the past two years, explained its benefits and limitations in an exclusive interview with *Daniela Zimmermann* of *European Hospital*.

Discussing developments in Intracardiac echocardiography (ICE), José Ribeiro, cardiologist at the thorax and circulation unit in Gaia Hospital Centre, Portugal, explained that recently the need for a different ultrasound tool to guide patient treatment beyond transoesophageal echocardiography (TEE) became clear. 'Consequently,' he added, 'a significant number of interventional cardiologists have started to use ICE.

'We still have limitations with ICE for structural heart disease, because we don't see all the structure in the same plan and need to navigate with a catheter inside the heart. That's why it's so important for 3-D imaging to guide procedures.

'We don't need too much imaging to guide the intervention for structural heart disease. But we need to have a good pre-procedure evaluation and to plan the procedure, and after that we only need specific steps to ensure procedure quality and check the results. If we can get the cardiac structures on 3-D, we have a significant advantage for guidance.

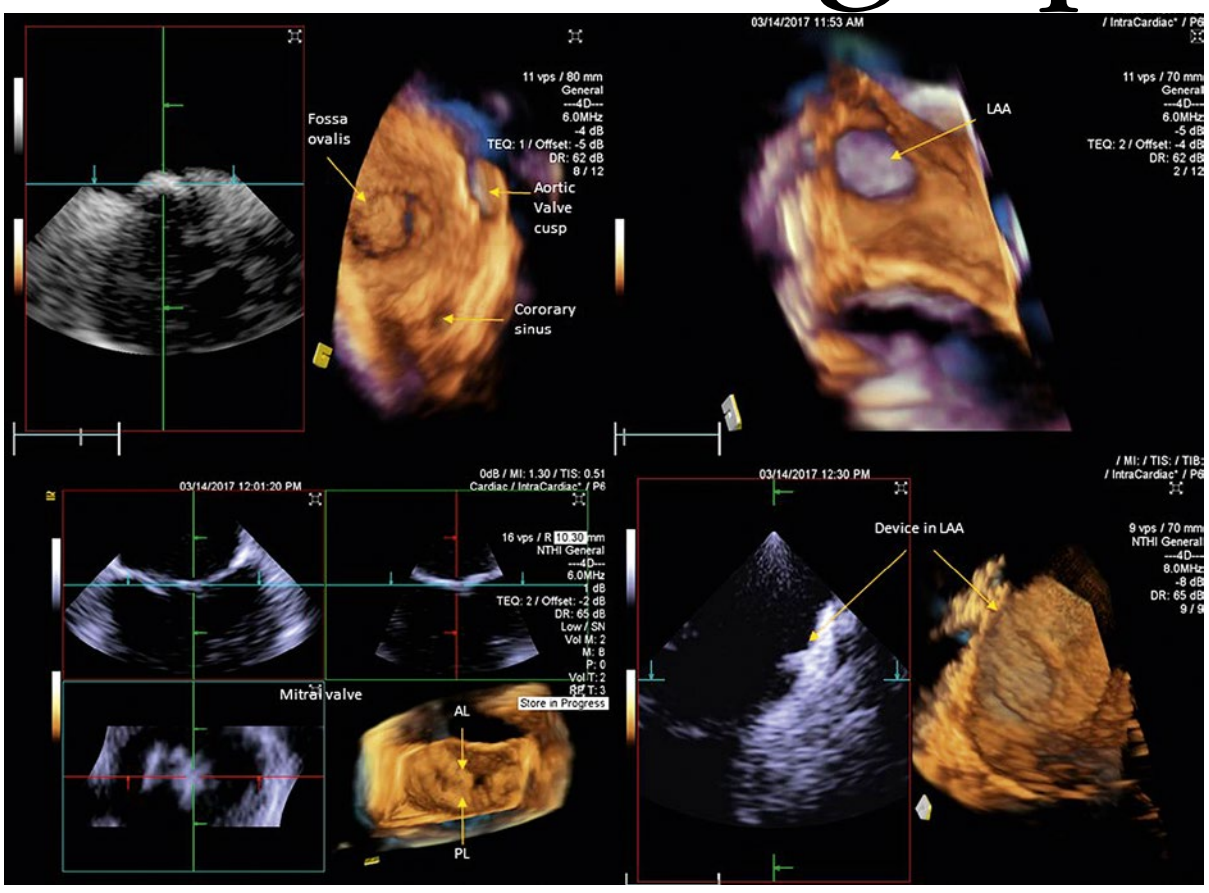
'We initially had a narrow angle catheter, which only enabled us to view small volumes of the heart. This is not enough to image entire structures, for instance a valve, left appendage or oval fossa. So we developed a new device with a wide opening angle; it's a 12.5-Fr catheter and this enables us to view significant volumes of the cardiac tissue, including the whole mitral valve. This development appears to be a great advantage for guidance.'

DZ: When using ICE, is the image in front of you and can you see the relation between the structures?

'Yes. When we have a volume, we can look inside and decompound it in a different 2-D plan to navigate more easily, which enables us to be more confident when doing the procedure.

'With a 3-D wide angle ICE catheter, we have the same benefits as with 2-D ICE, meaning we don't need an anaesthetist, the interventional cardiologist can do the intervention himor herself, by putting the catheter in the right place to see the heart.

'But we can also obtain a significantly higher amount of information and anatomy, so that the interven-



Images of intracardiac echocardiography obtained with Acunav V wide angle catheter (Siemens Healthineers); on 3D images we can see entire cardiac structures: on top right the fossa ovalis, on top left the left atrial appendage opening (LAA), on bottom right the mitral valve with anterior (AL) and posterior (PL) leaflets and on bottom left the device occluding LAA.

More people need nuclear cardiology training

Ischaemia: Advances in nuclea

Experts outlined approaches to ischaemia imaging during the recent British Cardiovascular Society conference. In a 'Detection of ischaemia by cardiac imaging in 2018' session, comparisons were made between solid state SPECT cameras, whether spatial resolution or visual assessment was of the greater importance, if CT-FFR offered advantages over CT perfusion, and the challenges in defining a gold standard of imaging ischaemia

Discussing 'Advances in nuclear ischaemic testing, from SPECT to PET and beyond', Dr Kshama Wechalekar, who heads Nuclear medicine and PET at the Royal Brompton Hospital in London, and is President of the British Nuclear Cardiology Society (BNCS), told delegates that advances in nuclear imaging with solid state technology offered improved ability to detect ischaemia. 'There is improved spatial resolution from multiple solid state CZT (Cadmium Zinc Telluride) detectors and therefore sensitivity is very high,' she explained. 'You can reduce the acquisition time at least by half with excellent quality and the equipment has a small footprint. The advantages of solid state detector cameras is that you can reduce the radiation dose by one third, have high sensitivity and resolution, an open design suitable for claustrophobic patients, and good image quality even in obese patients.'

President of British Nuclear Cardiology Society **Dr Kshama Wechalekar** leads nuclear medicine and PET at the Royal Brompton Hospital in London, where she specialises in heart/lung nuclear imaging. Her main interests lie in using hybrid-imaging techniques, such as SPECT-CT and PET-CT, to improve understanding of pathophysiological processes affecting the heart and lungs. She has special interest in cardiac sarcoidosis and other inflammatory conditions of the heart.

SPECT, PET and CMR

Recent studies have shown ability to do dynamic imaging offering potential in quantitative myocardial perfusion with SPECT, Wechalekar pointed out, adding that SPECT is less expensive than current PET and MRI.

'The future of SPECT Nuclear cardiac imaging,' she concluded, 'is in solid-state technology. Dynamic imaging, although technically challenging, can add value to MPI in the detection of ischaemia. Whilst PET is the most accurate imaging technique for ischaemia assessment and prognosis, it remains expensive and less accessible.' She also felt that the new tracer, Flurpiridaz, with results of phase III trials in the UK pending, might change the future of PET MPI.

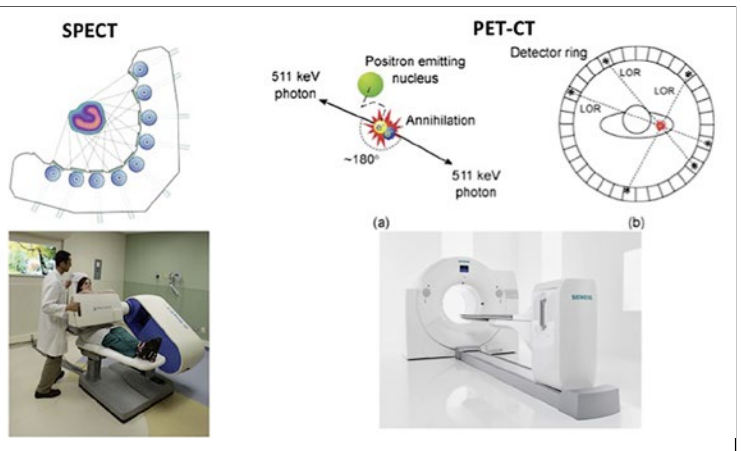
One area of concern was how to persuade more people to train in nuclear cardiology with falling numbers in the field. 'The BNCS Council is working hard to improve curriculum, organise level 1 and 2 training courses, and to identify centres that can offer nuclear cardiology training across the country that is easily accessible for trainees,' she said.

Dr Chiara Bucciarelli-Ducci is Consultant Senior Lecturer in Cardiology/non Invasive Imaging at the Bristol Heart Institute, University of Bristol, and co-Director of the Clinical Research and Imaging Centre (CRIC Bristol). She is currently one of the vice-presidents and chair of cardiac MRI of the European Association of Cardiovascular Imaging (EACVI).

Dr Chiara Bucciarelli-Ducci, Consultant Senior Lecturer in Cardiology/non Invasive Imaging Bristol Heart Institute, University of Bristol, explored the issue of quantitative versus visual assessment in CMR stress perfusion. She explained that stress CMR has been included in the ESC guidelines since 2014 (ESC revascularisation guidelines) based on evidence using visual assessment of ischaemia, rather than quantitative.

Bucciarelli-Ducci discussed pros and cons of both visual and quantitative assessment, limitations and opportunities to increase spatial resolution, and very recent studies showing that there is no difference in diagnostic accuracy visual vs. quantitative. Quantitative perfusion is promising, but the acquisitions and analysis need simplification to meet the need of a busy clinical service.

'CMR perfusion (visual) is a good clinical tool already,' she concluded, 'but can get better while quantitative CMR perfusion is evolving into faster and robust tools. While several methods are available, more in-vivo and clinical validation is needed with a number of studies in the pipeline.'



Single photon vs. Positron ET

Dr Marc Dweck is Senior Lecturer and Consultant Cardiologist at the University of Edinburgh and the Edinburgh Heart Centre. A British Heart Foundation Intermediate Clinical Research Fellow, he is a keen advocate of multi-modality cardiovascular imaging and is trained in echocardigraphy, carotid ultrasound, computed tomography (CT), cardiovascular magnetic resonance (CMR), PET/CT and PET/MR imaging.

Function addition can improve specificity

Dr Marc Dweck, BHF Reader in Cardiology and Consultant Cardiologist at the University of Edinburgh and the Edinburgh Heart Centre, posed the question 'CT-FFR/CT perfusion - neither or both?'

'CT Perfusion,' he acknowledged, 'is interesting, but I'm not sure how we are going to use it in clinical practice. With CT-FFR you get beautiful pictures, where you can look down the coronary arteries and see areas that are not getting enough blood. The advantage of this technique is that you can use it on a post-hoc basis, on scans where you are not sure if a lesion is obstructive or not, without any extra radiation or medication for the patient. This may be useful in lowering the rates of patients being sent

(ICE) has benefits

tional cardiologist can do the whole procedure without having to navigate with the image catheter. We can put the catheter in the right place, and then we don't need to move it to see what we need to see.'

What are the benefits of not having to move the catheter?

'Moving the catheter to view the cardiac structures means more work, more time, more risk and more radiation.

'In the interventional lab, we always use angiography and ultrasound. Angiography, i.e. radiation imaging, helps us to carry out the procedure and navigate to place the ICE catheter inside the heart. If we don't need to move the catheter because we can see everything at once, we of course also need less radiation.

'If we have a technology that gives us everything with the catheter in the same place, it's much better.'

Many specialists are needed in such an intervention. One day, could just one person do this?

'That's the big point. But we need to train interventional cardiologists, to change their mind-set. They typically use angiography and ignore ultrasound.

'However, this is changing now. Everything is changing in the interventional lab. We are using TEE in a significant number of procedures; but with TEE we also need specialists. With ICE, we can do everything while the patient is awake, without discomfort and anaesthesia, and with fewer people inside the room and less radiation.

'In the lab, for ICE guidance we use the echocardiography machine to direct the image and ICE catheter manipulation beyond the angio room equipment. In future, we could have all the controls on the table – connecting angio and ultrasound controls. Also, we need to improve the imaging display software, with specific play sets for detailed procedures, to give the right plans for each interventional procedure.

'Right now, in our hospital, we simultaneously use display ultrasound imaging and angio imaging on the same screen. We can switch to all the positions we need, but we need lots of training to be able to see it.

The learning curve for interventional cardiologists is long. Some interventional cardiologists already have experience with 2-D imaging, and they have a significant advantage to give the final step to use 3-D imaging in ultrasound. The learning curve is more important when you are using angio only.'

For which cases do you use TEE and ICE?

'In our lab we check all patients in the echo lab in a selection process and, when we are very confident about the pathology or anatomy, we use the ultrasound image (TEE or ICE) for guidance and to improve confidence during the procedure.

In simple cases, such as ASD or PFO closure, we use ICE. As mentioned earlier, ICE gives us many advantages - no anaesthesia needed, more comfort, etc. For more complex cases we must decide how much imaging we need.

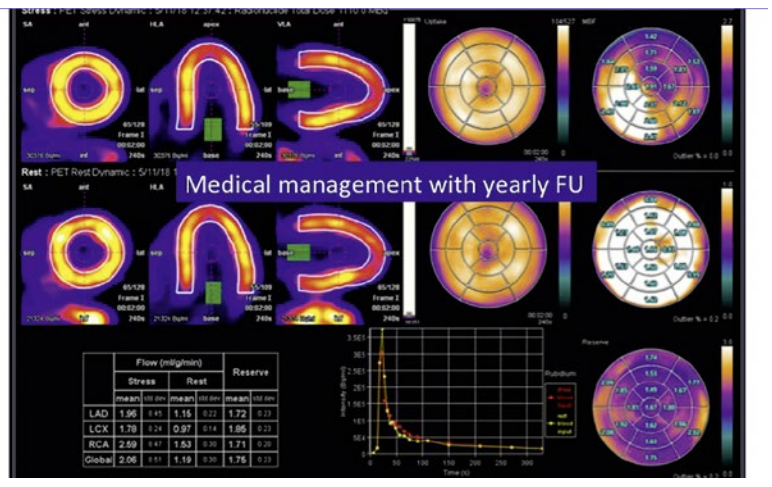
'We also use ICE in normal mitral valve repair and left a; we have initial experience with this wide angle 3-D ICE catheter that crosses the inter-atrial septum to scan left side structures, for instance.

'So far, our experience with ICE is limited. But even with more experience, in complex cases we tend to prefer the technique or imaging tool with which we have more experience. So TEE may still be preferred in such scenarios. The main limitation of ICE is lack of experience with the technology. In addition, if the case is too complex, we may need to cross with the catheter to the left side, so we need to move the catheter to be sure.'

'ICE could be useful in some patients who cannot be imaged with TEE. Both methods are alternative. ICE is a step forward, especially with this new dimension – 3-D ICE. But,' he concluded, 'in the future we need to check what's the best option for each patient.'

José Manuel Coelho Ribeiro MD directs the Thorax and Circulation Unit at Vila Nova de Gaia Hospital Centre in Portugal. Having graduated from Oporto medical school in 1992 he became a cardiology specialist in 1996, which was followed by an echocardiography fellowship at Onze-Lieve-Vrouwziekenhuis in Aalst, Belgium. He also became a member of the Portuguese Cardiology College. Since 2001, he has led the echo lab (with 9,600 studies in 2017) and, from 2006, has been cardiology consultant in the Espinho Hospital Centre at Vila Nova de Gaia, where he has implemented new techniques, including transoesophageal echocardiography, as well as coordinated several telemedicine projects.

r imaging



Quantitative myocardial perfusion reserve with Rb-82 PET

to the cath lab following CT.' Patients most likely to use CT-FFR, he added, are those with borderline lesions, though he stressed the key lies in a patient's history and only using CT-FFR in patients with recalcitrant angina symptoms.

CT is a powerful imaging technique that informs about coronary artery anatomy (plaque burden, stenosis severity, plaque characteristics), he concluded, but emphasised that the addition of functional technique to the scan protocol can improve its specificity to identify obstructive stenosis, providing a comprehensive assessment of anatomy and function.

With CT perfusion, radiation dose is increased, while CT-FFR has increased cost, though CT-FFR potentially fitted in better with patient workflows.

Professor Darrel Francis discussed the problems of computed tomography in the presentation 'Ischaemia detection - are all our ideas completely wrong?' He pointed out that all previous speakers had described sensitivities and specificities, concepts that are meaningful only if ischaemia is dichotomous (present versus absent). His audience poll revealed cardiologists unanimously considered ischaemia to be a continuous gradation rather than dichotomous. mn

Professor Darrel Francis is Professor of Cardiology, Imperial College London. His work in ischaemia has included the ORBITA trial of revascularisation and the BRAVO trial of automated haemodynamic optimisation of cardiac resynchronisation therapy pacemakers.

At the heart of research

Continued from page 9

London, said: 'For about 1 in 4 patients with DCM we can find a genetic cause.

But that leaves us with hundreds of thousands of people with DCM that we cannot explain, which hinders our ability to diagnose and treat the patients or help their families. 'There are currently no targeted treatments that are specific for DCM but, as we get a better understanding of the genes which cause the condition, we can hope to develop new treatments which target these genes and pathways.' Professor Sir Nilesh Samani, Medical Director of the British Heart Foundation, which has delivered £2m funding for the study, said: 'In many cases, we can track the inheritance pattern and test family members of people with inherited heart conditions. But unfortunately, genetic testing is often not helpful for people with DCM, as we only know about a small number of genes which cause the condition.' In 2011, Professor Cook and his team established the genetics and genomics group at NHLI and have developed and applied unbiased, integrated systems genetics and genomics approaches combined with high-resolution cardiovascular phenotyping to identify new genes and mechanisms for cardiac hypertrophy and dysfunction.

The team has used genome-wide association in humans to identify new loci and genes for DCM and has already identified titin as the commonest genetic cause of DCM.

Coronary angiography will lose diagnostic value

The changing face of imaging in cardiology

While the question is still debated as to whether MRI is the better CT, along comes a potential game changer – a new data based 3-D reconstruction method of heart anatomy and function that aims to replace diagnostic coronary angiography. In the near future not only adult patients with coronary heart disease could benefit from this new technique but also children with complex congenital heart defects. Meanwhile imaging is conquering the cardiac operating room (OR).

The physician, using smart glasses, in the virtual space has just removed the aorta at its root from the heart to examine it separately. Observers can follow on conventional screens. Courtesy: S. Engelhardt

Report: Emilie Hofstetter

Long before coronary heart disease (CHD) manifests its presence on an ECG, CT and MRI can detect it due to low perfusion caused by a stenosis of the coronary vessels. Dr Bettina Baessler, radiologist and researcher at the University Hospital Cologne, Germany, looks into multiparametric imaging strategies. She considers both techniques complement one another although MRI definitely produces images that are 'more beautiful, almost works of art'.

Professor Ulf Teichgräber, Head of Radiology at University Hospital Jena, Germany, agrees and thus predicts the demise of cardiac angiography. His opinion is corroborated by the recently completed SYNTAX III study, whose results will be presented at the Transcatheter Cardiovascular Therapeutics Symposium 2018 in San Diego in September. A team comprised of a radiologist, cardiologist and surgeon (Heart Team A) evaluated the angiogram of a patient, calculated the SYNTAX II score and decided on the type of therapy, either invasive or non-invasive.

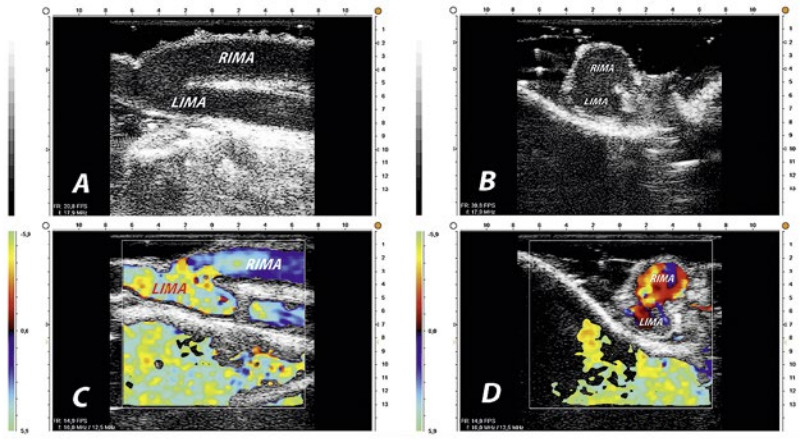
The team members then saw the multislice CT (MSCT) scan with 3-D reconstructed coronary vessels and the relevant fractional flow reserve (FFRCT) and could either confirm or revise their decision. A second team (Heart Team B) of those professionals received CT and FFRCT of the same patient first. The team members calculated the Syntax III score, decided on the type of therapy and then saw the angiogram in order to either confirm or revise their decision. 'The Syntax score was designed to inform the decision "invasive or non-invasive", based exclusively on anatomical features,' Teichgräber explained. 'Syntax II took comorbidities into account and now Syntax III includes a functional component – FFRCT. Thus coronary angiography will lose importance in diagnostics and therapy planning.'

Non-invasive first

To date, only the California-based HeartFlow Inc. can calculate FFRCT. Based on data obtained in a conventional CT, the company's software, using flow mechanics, can reconstruct heart, aorta and coronary vessels in terms of geometrics as well as pathophysiology and function in 3-D. Moreover it visualises the flow and can thus show whether a haemodynamically relevant blockage is present, i.e. whether the patient needs a stent or a bypass.

In 2015, Professor Pamela S Douglas, cardiologist and Head of Multimodal Imaging at the Duke Clinical Research Institute in Durham, North Carolina, USA, showed the potential benefit of this method using 584 patient cases from 11 hospitals. Ten patients with suspected CHD underwent diagnostic cardiac catheterisation, but the suspicion was confirmed only in three patients – seven underwent unnecessary catheterization. Six out of ten patients with suspected CHD, whose FFRCT was determined first, did not need angiography. In three out of the four patients who did receive angio, the suspicion was confirmed – i.e. only one patient underwent an unnecessary angiography. 'This feasible and safe method shows a significantly lower rate of unnecessary invasive angiographies,' Douglas confirmed. Investors seem to buy in: HeartFlow, which today is already cooperating with the Big Three – GE, Siemens, Philips – recently raised USD 240 million to further develop the technology, launch new studies and drive commercialisation of its product.

To establish 3-D imaging in congenital heart disease treatment, paediatric cardiologists Animesh Tandoon and Tarique Hussein founded VARYFII Imaging, LLC, in Dallas, USA. They construct complex anatomical models of the individual patient's pathologies using MRI or CT data. Cardiologists as well as surgeons can enter the virtual and augmented realities of the anatomical models with the help of data headsets to lift certain structures, analyse and reposition them and thus devise the best strategy to correct the heart defect prior to surgical intervention.



Y-conduit of right and left internal thoracic artery in epicardial ultrasound. A: 2-D Long axis view, B: 2-D short axis view, C: Colour Flow Mapping long axis, D: Colour flow short axis. Courtesy: Di Giammarco

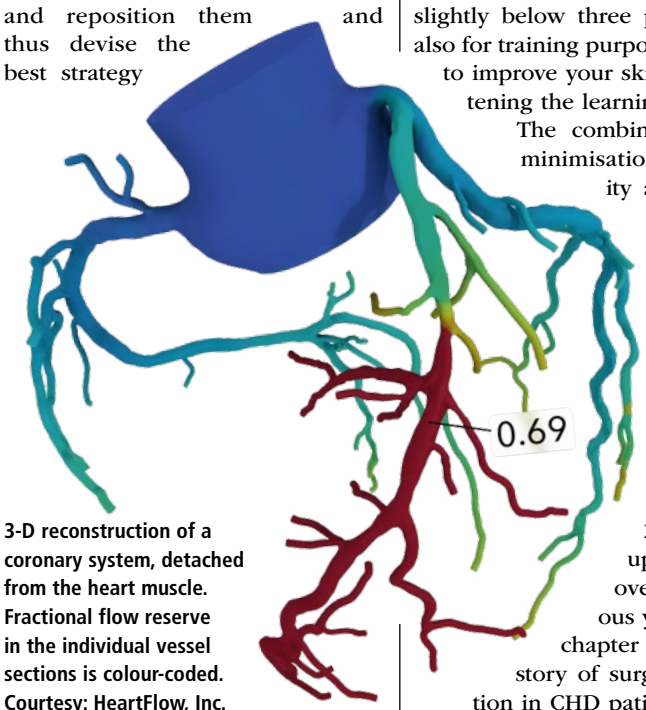
'Our heart beats in 3-D, so why not examine it in 3-D?' asks Dr Sandy Engelhardt, researcher at the Computer-Assisted Surgery Group at the Department of Simulation and Graphics in Otto von Guericke University, Germany. In addition to treatment planning and education she envisages a further application of this new technology: informing the parents of the young patients.

The flow must continue

Imaging has arrived in cardiac surgery – during the intervention itself and combined with flow measurements. Professor Gabriele Di Giammarco, cardiac surgeon at Gabriele D'Annunzio University Hospital in Chieti, Italy, considers the combination of high-frequency epicardial ultrasound (ECUS) and transit time flow measurement (TTFM) in a single device 'decision making' and explains: 'Hard calcifications in the aorta, I can feel. I do not feel the dangerous soft plaques. With MiraQ, I see them in intraoperative ultrasound, can adapt my strategy and perform surgery in no-touch technique and off-pump.'

Dr Daniel Wendt, Managing Senior Physician at the Cardiac Surgery Department of University Hospital Essen, Germany, uses intraoperative flow measurement of newly created bypasses not only for quality assurance purposes – he records a follow-up intervention rate of slightly below three percent – but also for training purposes: 'It's a tool to improve your skills, helps flattening the learning curve.'

The combination of risk minimisation and quality assurance has proved successful. In 2017, the Oslo-based manufacturer Medistim sold products and procedures worth NOK 229.8 million, up 14.6 percent over the previous year – another chapter in the success story of surgical intervention in CHD patients.



3-D reconstruction of a coronary system, detached from the heart muscle. Fractional flow reserve in the individual vessel sections is colour-coded. Courtesy: HeartFlow, Inc.

The future POCT heart attack test

On the way: mobile cMyC analysis

Experts report that a new blood test to diagnose heart attacks could be carried out on a hand-held device in the not-too-distant future.

Report: Mark Nicholls

The test, devised by a team at Kings College London, uses similar technology to the troponin test, but instead analyses cardiac myosin-binding protein C (cMyC).

In research presented at the British Cardiovascular Society conference in Manchester, UK, this June, Dr Tom Kaier, BHF Research Fellow, explained that levels of cMyC in the blood increase more rapidly after a heart attack and to a higher extent than troponin. With this offering the opportunity to rule out a heart attack in a higher proportion of patients instantly, the research team believes it has a role in providing a swift diagnosis in Accident & Emergency (A&E) departments.

Scientists are optimistic that this relatively straightforward test could be used as a hand-held point of care test (POCT), and avoid samples being sent to the laboratory.

cMyC outperformed troponin

Kaier, who was among the lead researchers, emphasised the importance for doctors and patients to know, as early as possible, who has had a heart attack and who has not.

'Now that we know this test is sensitive enough to give an almost immediate heart attack diagnosis,' he said, 'we need to work on developing a testing device.'

As work on developing a POCT device continues, the team hope that it could be used in wards - or ambulances - within five years, replacing time-consuming despatch of samples to hospital labs.

Trials of the test have been conducted around Europe by international collaborators. In Denmark, blood was taken from 776 patients travelling to hospital by ambulance, which the King's College London researchers then tested for cMyC protein.

In patients who had suffered heart attacks, Kaier said, the protein was present in high enough concentrations 95% of the time for an on-the-spot diagnosis.

The cMyC test outperformed the existing troponin test, which diagnosed only around 40% of patients in this way, mainly because troponin takes longer to reach detectable levels in the blood after a heart attack.

'A stand-out feature is cMyC's ability to more effectively triage patients,' Kaier said. 'This distinction is likely related to the documented greater abundance and more rapid release profile of cMyC. If used on a POCT platform, cMyC could significantly improve the early triage of patients with suspected AMI.'

Better rule-in and rule-out rate

Figures show that more than 65% of people who attend A&E with chest pain have not had a heart attack, though all will receive an ECG and a blood test to measure troponin levels.

With the cMyC blood test shown by the KCL team to have a better rule-in and rule-out rate for heart attack, the research team believes this will be a valid tool in reassuring patients sooner and avoiding unnecessary hospital stays for further tests.

In part, the research has been funded by the British Heart Foundation, which said the initial results from the cMyC test look 'very promising' for patients and acknowledges that it could lead to quicker diagnosis and treatment, or see patients reassured and discharged.

However, BHF Associate Medical Director Professor Jeremy Pearson stressed that further research was necessary before cMyC could be recommended as a replacement for the troponin test.

Dr Tom Kaier is a BHF Research Fellow, having previously been a Specialist Registrar in Cardiology at Barts Health NHS Trust and the Royal Free London NHS Foundation Trust in the UK. .

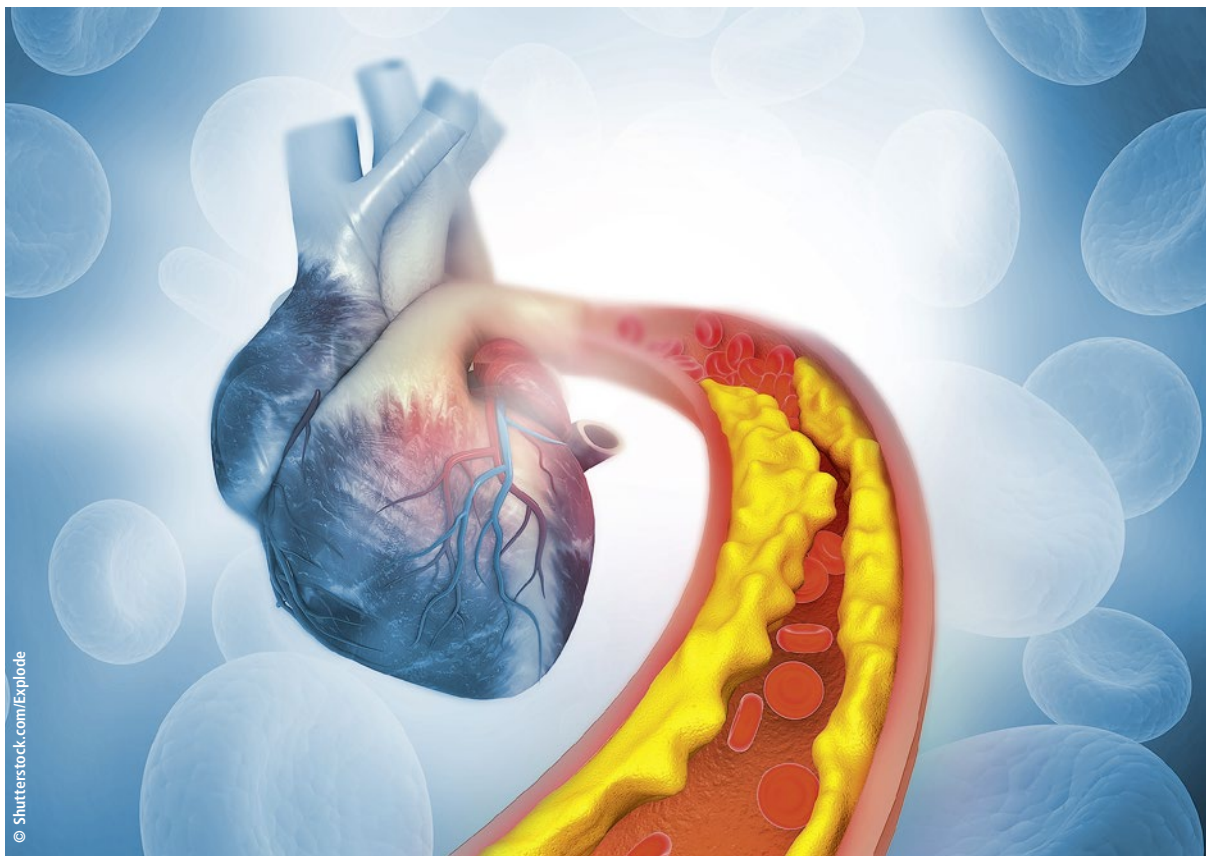
Arrhythmia news from CMR 18

Multidisciplinary cardiology

Eminent Spanish cardiologist highlights the evolving role of imaging in ventricle arrhythmias treatment

Report: Melisande Rouger

Intervention in ventricular arrhythmia has improved dramatically over the past three decades thanks to advances in imaging and cooperation between cardiology and radiology, according to Professor Josep Brugada MD, director of the paediatric arrhythmia unit at Sant Joan de Déu Hospital in Barcelona.



'Echocardiography, CT and MRI, combined with cardiology,' he said, 'have revolutionised the field into what it is now a truly multidisciplinary field.'

Cardiologists have learned to use echocardiography. Collaboration with radiologists has enabled them to understand ventricular tachycardia and ventricular fibrillation, two life-threatening diseases that are most commonly associated with heart attacks or scarring of the heart muscle from previous heart attack.

As a result, knowledge of physiopathology and arrhythmia mechanisms has grown over the past thirty years, first with understanding the location of arrhythmia, a parameter that remains crucial for treatment.

Decades of developments

'Thirty years ago, we were performing diagnostic electro-physiological studies, and at that time our relationship with imaging was very simple – we just used X-ray. But in the late 1980s, we understood that we could start treating these patients and that we could start targeting the points that we identified as the points of arrhythmia, and with more and more accuracy to understand where these points were,' he explained.

Using X-ray and echocardiography combined with the electric signal first enabled very simple arrhythmic substrates to be located. Cardiologists soon understood that they needed, and could get, more information from imaging.

In the late 1990s, CT enabled the visualisation of more complex arrhythmia substrates, such as ventricular tachycardia. 'It was not enough to use echocardiography anymore. At that time we needed to have information on the position and size of different structures, for instance the pulmonary veins. We used the CT scan to help us to do just that. That was a very important step,' Brugada pointed out.

Inside cardiac tissue

Ten years later, around 2010, the medical team realised that they had to go even further in their understanding of arrhythmia, beyond anatomic knowledge; they also needed to know what was inside the heart tissue.

'We wanted to see how the tissue is built in the heart, to assess tissue structures and understand how different elements of cardiac tissue can be identified as normal or abnormal areas. This can only be done with nuclear magnetic resonance imaging. Only then did we begin to understand what the true nature of the tissue is,' Brugada said.

MRI enables us to depict details in both ventricles. Checking the left ventricle, especially, remains crucial because of the various potential origins of arrhythmia. 'If you have a myocardial infarction, we know the abnormal tissue can be located in the endocardium site and even the mid-myocardium site. So you need to see the structure of this tissue. That's why all the efforts are now focused on understanding how the tissue is structured and built in the ventricles.'

MRI provides information on the nature of tissue, and, used in combination with electrical mapping system, helps identify electrical pathways or channels that may cause arrhythmia. Unveiling the electrical anatomy of pathways in the muscle is crucial at the time of eliminating arrhythmia, Brugada explained.

'Using MRI, to extract anatomic information, and our mapping system, which enables us to identify where the electricity goes through, we can determine the exact point that may be responsible for arrhythmia. We can then target this point with radiofrequency and burn it, and thus prevent the electricity going through the pathways that cause arrhythmia.'

Major contribution

MRI is also used to guide intervention and correct potential error; this is a new and major contribution of imaging to arrhythmia treatment.

'You need to integrate this imaging and perform 3-D imaging of the heart because you want to see exactly what is happening,' Brugada explained. 'That's a technique we use every day, and increasingly to treat atrial arrhythmia in atrial fibrillation,'

The main interventional treatment of AF consists in blocking the pulmonary veins using radiofrequency, i.e. by burning around the veins to create a line of electrical block. During the procedure, gaps may occur in these lines of block; these breaches can only be spotted on MRI. Being able to pick these gaps will lead to redoing the procedure and improving treatment success and patient outcome. In the future, MRI will continue to improve treatment efficiency in AF, a disease that affects millions of patients worldwide, and ventricular tachycardia patients, whose only chance of survival is to receive adequate treatment. 'There are fewer cases of ventricular tachycardia than AF, but these are very severe patients who need a cure. It is fundamental for their survival and the only thing we can do right now is to target the right electrical pathways.'

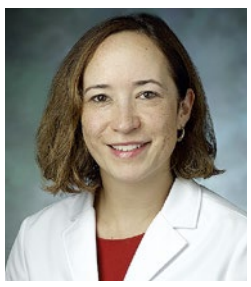
Professor Josep Brugada studied medicine at the University of Barcelona, Spain, before moving to the University of Montpellier, France, to specialise in cardiology. He continued training in Maastricht, Netherlands, to specialise further in the clinical and basic aspects of cardiac arrhythmias, and he worked simultaneously in the basic and clinical electrophysiology laboratory. Brugada then became Assistant Professor at the University of Limburg and was the first foreign established investigator of the Dutch Royal Academy of Arts and Sciences. In 1991 he returned to the hospital at the University of Barcelona, where he became professor of medicine, head of the arrhythmia unit, and of cardiology, director of the thorax institute and finally medical director. He is now professor of medicine, director of the paediatric arrhythmia unit at Sant Joan de Déu Hospital in Barcelona.

Session arrest i

MRI has a central role in picking up myocar nary disease, a condition that particularly a with potentially fatal outcome.

Heart attack in women presents differently than in men and requires a different approach when it comes to detection and prevention, according to Allison Hays, a cardiologist and assistant professor at the Johns Hopkins University School of Medicine, speaking at CMR 2018 meeting in Barcelona.

'Women don't present typically with chest pain, but rather with tiredness or shortness of breath. When they eventually come in for diagnosis, women have much less rates of having abnormal cardiac catheterisation test, which shows degree of stenosis in coronary arteries. So, much more commonly, they



Allison Hays MD is a general cardiologist and interim Director of Echocardiography Programs at the Johns Hopkins Heart and Vascular Institute. She is also an assistant professor at the Johns Hopkins University School of Medicine. Having graduated from Stanford University she received medical training at the Columbia University College of Physicians and Surgeons. Following her residency at the New York Presbyterian Hospital at Columbia Hays pursued cardiology fellowships at New York University Medical Center and at the Johns Hopkins University School of Medicine. Today she studies ways to use non-invasive imaging to detect cardiovascular disease. In terms of research, Hays uses cardiac MRI as a tool to study coronary and systemic endothelial function.

EUROPEAN HOSPITAL
European Hospital Verlags GmbH
Theodor-Althoff-Str. 45,
45133 Essen, Germany
Phone: +49 (0)201 87 126 850
Fax: +49 (0)201 87 126 864
E-mail: info@european-hospital.com
www.healthcare-in-europe.com

Editor-in-Chief: Brenda Marsh
Art Director: Olaf Skrober
Editorial team:
Wolfgang Behrends, Sascha Keutel, Brigitte Dinkloh, Marcel Rasch
Senior Writer: John Brosky
Executive Director:
Daniela Zimmermann
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Correspondents
Austria: Michael Kraßnitzer, Christian Pruszinsky.**China:** Nat Whitney **France:** Jane MacDougall. **Germany:** Anja Behringer, Eva Britsch, Annette Bus, Walter Depner, Emelie Hofstetter, Cornelia Wels-Maug. **Great Britain:** Brenda Marsh, Mark Nicholls. **Malta:** Moira Mizzi. **Spain:** Mélisande Rouger, Eduardo de la Sota. **The Netherlands:** Madeleine van de Wouw. **USA:** Cynthia E. Keen, i.t. Communications, Lisa Chamoff.

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Representatives
China & Hongkong: Gavin Hua, Sun China Media Co, Ltd.
Phone: +86-0755-81 324 036
E-Mail: gavin_hua@163.com

Germany, Austria, Switzerland:
Ralf Mateblowski
Phone: +49 6735 912 993,
E-Mail: rm@european-hospital.com

France, Italy, Spain: Eric Jund
Phone: +33 493 58 77 43,
E-Mail: ej@european-hospital.com

GB, Scandinavia, BeNeLux:
Simon Kramer
Phone/Fax: +31 180 6200 20
E-Mail: sk@european-hospital.com

Israel: Hannah Wizer, International Media Dep. of El-Ron Adv. & PR Co., Ltd.,
Phone: +972-3-6 955 367
E-Mail: hw@european-hospital.com

South Korea: CH Park, MCI
Phone: +82 2 730 1234,
E-Mail: mci@unitel.co.kr

Taiwan: Charles Yang,
Phone: +886 4 232 236 33,
E-Mail: medianet@ms13.hinet.net

USA & Canada:
Hanna Politis, Media International
Phone: +1 301 869 66 10,
E-Mail: hanna@media-intl.com

Heard at CMR 2018

n highlights cardiac n women

rdial infarction with non-obstructive coro- ffects women but is often left untreated,

do not have disease in the coronary arteries,' Hays explained.

Instead, women who suffer a heart attack usually present with myocardial infarction with non-obstructive coronary disease (MINOCA), a much less common condition in men. This difference suggests that biology of the coronary arteries differs greatly between sexes. Women have a much higher incidence of microvascular diseases, i.e. the very small vessels that are embedded into the heart muscle itself.

Worse prognosis for women

Treatment usually includes lifestyle modifications and traditional ways to lower risk factors such as blood pressure and high cholesterol. Nonetheless, heart attack has a worse prognosis in women than men, because it is generally not treated as aggressively as it should be, Hays argued.

'A lot of women don't have complete heart blockages and sometimes they're left untreated. So it's very important to recognise that even when a woman comes in with a heart attack and they don't have heart blockages that are detected on cardiac cath, it's very important that you still treat them for the small vessels disease aggressively with heart medication,' Hays said.

A main focus of CMR 2018 was to highlight the different and atypical presentation of women compared to men when it comes to heart attacks and how they can be detected, prevented and addressed in women, to improve outcome in the future.

Although cardiac arrest is the first cause of death in women as well, it was the first time the conference featured a dedicated session on the topic, probably because women are now better represented in the organising societies, Hay believes.

'In the last two years of the Society for Cardiovascular Magnetic Resonance, membership of women has grown significantly, going up from 20% to 40% today. So women are now more represented and more involved. I myself was one of the organisers, and found it was important to talk about that issue. The session was well attended, and we've had very good questions from the audience. I think this topic should be there every single year, because there's a lot of research in that area,' she said.

Stress MRI is a good tool for women

Awareness of that issue among the medical field must be increased, and the approach in detection must change, particularly regarding stress perfusion MRI, because this is an ideal tool to image heart disease in women, Hays believes. 'Some stress tests are better tailored to women because they are more sensitive. Stress MRI is particularly suited to heart attack detection in women because it's better at imaging microvasculature. EKG is not so sensitive for women and you can miss a lot. The same is true for CT, because you're just taking pictures to know how much narrowing or blockage there is, but it does not capture how much small vessel disease you have. Both modalities miss a lot of disease in women,' she pointed out.

The novel field of non-contrast MRI, which uses T1 and T2 mapping, may be an additional tool to detect areas of microvasculature perfusion in women. The technique has a lot of prospects but it is still a very new area of research and requires more investigation, Hays underlined. In the USA the Women's HARP study, a multi-centre, diagnostic observational study that aims to compare perfusion MRI results of women with heart attack to cardiac catheterisation techniques using optical coherent tomography will bring more knowledge of MRI's value within the next two years. It will also provide information on plaque inflammation and see whether this correlates with microvascular abnormalities. 'That will be interesting, to determine the reasons why there is microvascular dysfunction,' Hays said. MRI is usually less available than other modalities, but it is worth the extra effort to find centres of excellence because of the unique insights it offers, and not just in microvasculature, she believes. 'CT and nuclear tests are not so sensitive to image microvasculature. MRI plays a critical role not only for microvasculature disease, but also for heart failure, since a lot of women have heart failure with preserved injection fraction.'

mr

HemoDynamic Analytics in Ultrasound

A new tool box enhances heart failure diagnosis

One of the challenges for every echocardiography lab is the technically difficult patient. Conventionally, labs use contrast agents to enhance endocardial border visualization. The application of contrast agents increases the exam time, resources and costs. Additionally, the use of contrast turns a previously non-invasive exam into an invasive procedure.

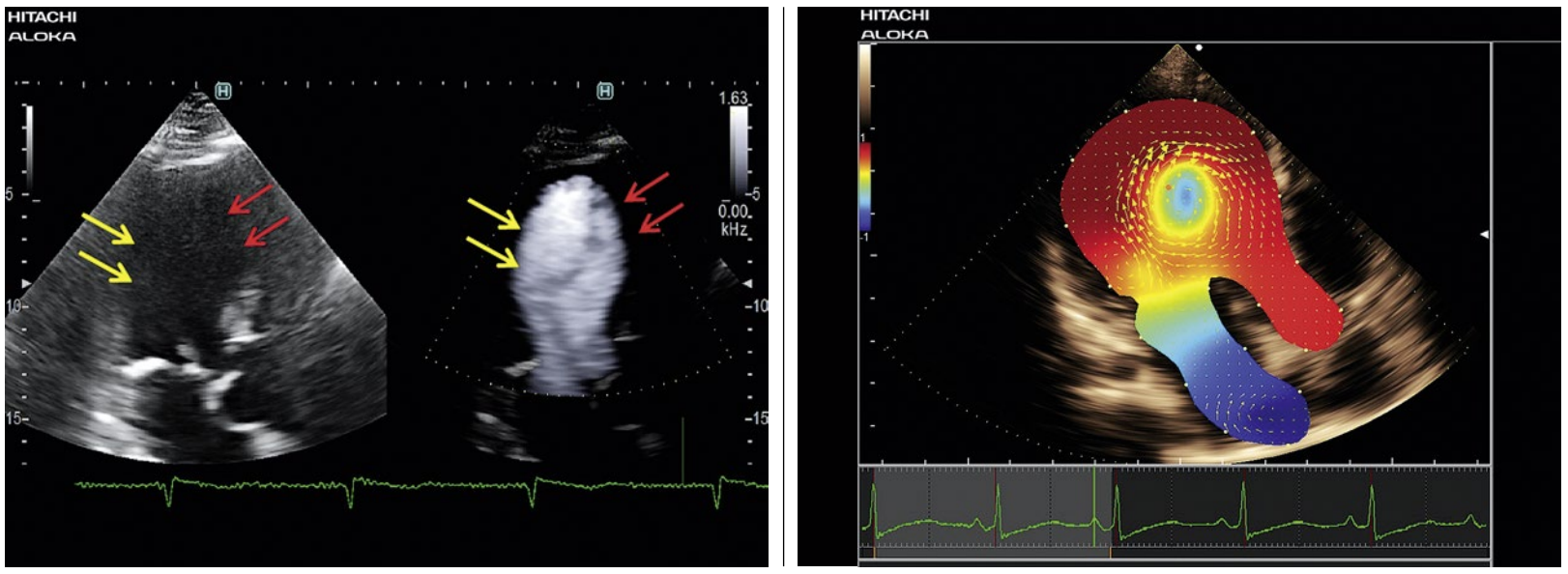
Hitachi Healthcare has now developed a collection of cardiovascular analytic tools called HemoDynamic Analytics (HDAnalytics). These tools can be used for evaluation of the left ventricle (LV) when visualization is limited. One of the main applications of the collection, LV eFlow was designed to demonstrate the discrimination between the blood flow and the cardiac tissue and offer an alternative to contrast agent use in some cases.

LV eFlow is a high-definition left ventricular cavity blood flow imaging mode which substantially improves spatial and temporal resolution for a better visualization of the endocardial border in the left ventricle. The new tool operates with higher sensitivity and resolution than conventional methods. LV eFlow may change a technically difficult study into a diagnostic exam without using contrast agent.

Head-to-head with echo contrast

Dr. Zuyue Wang and technologist Marvin Tyson of MedStar Washington Hospital Center had an opportunity to use this technology in their practice over a period of 3 months. Their protocol included identifying patients that were candidates for contrast agents due to the difficulty in visualizing the endocardial border of the left ventricle. LV eFlow was added to the exam protocol for this patient set. Following the exam, the quality of the endocardial border delineation was evaluated by comparing the LV eFlow images with the images using contrast agents.

Dr. Wang and Marvin Tyson compared LV eFlow and echo contrast agents in patients with suboptimal image quality and were impressed with the results. They found that "LV eFlow was comparable to echo contrast in improving visualization of difficult-to-image segments in selected patients". Additionally, they found "a markedly more precise endocardial border delineation" and stated that "contrast agents should only be utilized when LV eFlow fails to enhance the endocardial borders".



Left: LV eFLOW – technically difficult patient; right: VFM – relative pressure with a dilated cardiomyopathy. Source: Hitachi Medical Systems Europe

Vector Flow Mapping & Dual Gate Doppler

Another tool in the HDAnalytics collection is Vector Flow Mapping (VFM), a novel and validated application that allows users to assess cardiovascular blood flow distribution in an observation plane. This non-invasive technique is derived from the Color Doppler velocity data and generates the velocity fields on the 2D image. This allows to visualize, measure and analyze different parameters from the blood flow distribution. For example, energy loss which is the rate of energy dissipation due to blood viscosity, increases where turbulence flow occurs. In addition, wall shear stress, relative pressure and vortex characteristics can be evaluated.

The Dual Gate Doppler (iDGD) generates a full Fast Fourier Transform (FFT) analysis and display from two separate sample gates allowing measurements from two different locations during the same cardiac cycle. Hitachi Artificial Intelligence technology enables automatic sample gate placement and measurement at appropriate heart beats, resulting in 5 seconds to get E/e' (83% shorten time compared with conventional measurement). Furthermore, iDGD works well for PW/PW and TDI/TDI combinations.

2D tissue tracking (i2DTT)

With 2D Tissue Tracking (i2DTT), the HDAnalytics set also provides an advanced tool which allows users to track the displacement of the cardiac tissue by using a novel and accurate algorithm of "Speckle Tracking". Doppler based methods such as TDI are limited in evaluating the displacement velocity of the tissue due to angle dependency. i2DTT allows the detection of velocity components perpendicular to the beam which is impossible with conventional Doppler techniques. Tracking image by image, the natural patterns of the cardiac tissue in B-Mode permits the user to quantitatively evaluate the movement and the thickening of the myocardium. i2DTT provides precise quantitative information such as longitudinal and radial strain, torsion rotation angle, displacement, wall thickening and various other parameters to visualize, quantify and analyze myocardial mechanics. Applications include cardiac function analysis, resynchronization therapy, cardiomyopathy, stress echo and other global and regional studies.

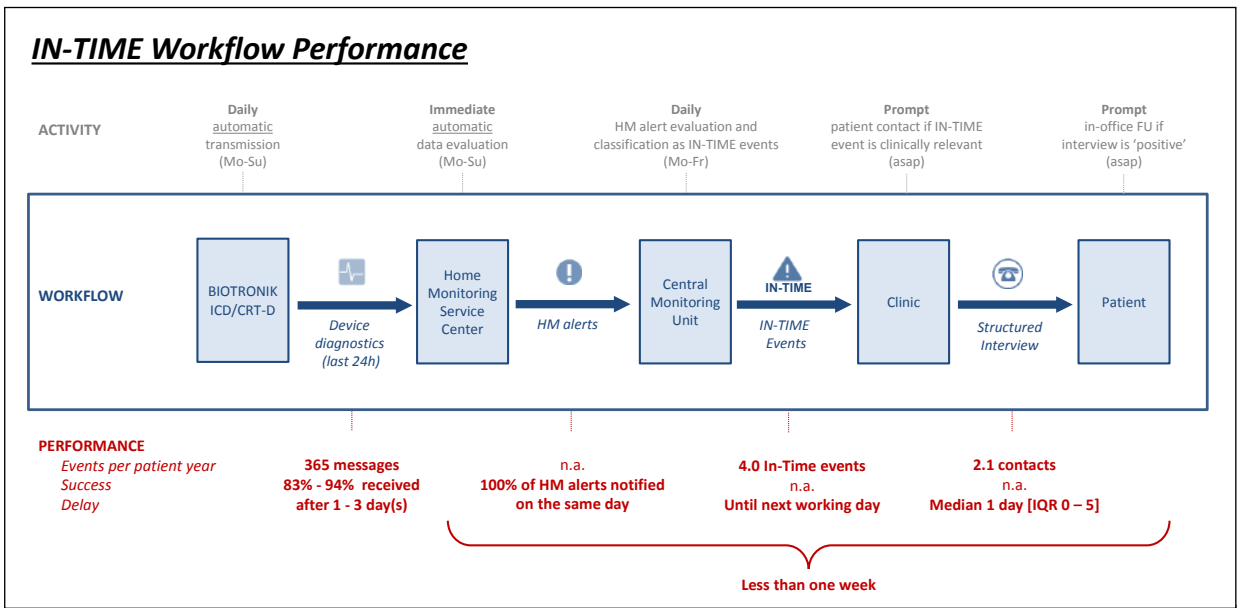
New analysis suggests workflow is key in remote monitoring

It's time to look again at IN-TIME

As the world's largest cardiology congress gets underway in Munich, it's worth looking back to previous ESC sessions to see how scientific debates have evolved. At ESC 2016, held in Rome, REM-HF investigators presented data suggesting remote monitoring in implantable cardiac devices offered no added clinical benefit. Two years on, there are new reasons to re-examine that conclusion, with a recent analysis of the IN-TIME trial suggesting the key to remote monitoring benefits might be found in workflow processes.

Published in *The Lancet* in 2014, the IN-TIME study is the only trial, to date, to have demonstrated a clear benefit of implant-based remote monitoring in heart failure (HF) patients – showing a more than 50% reduction in all-cause mortality – while eight other studies included in a 2015 meta-analysis, and three other recent trials, found no significant clinical benefit.

However, IN-TIME was also the only implant-based remote monitoring trial using a transmission technology that sent daily updates to a central monitoring unit. By contrast, REM-HF used technology that transmitted implant data on a weekly basis. So why does IN-TIME show positive results when other remote monitoring studies don't? What is so fundamentally different in its methodology that might account for its results?



Multiparametric data

This is a central question in the recently published *Remote Monitoring and Clinical Outcomes: Details on Information Flow and Workflow in the IN-TIME Study* by Husser et al. The authors note that IN-TIME featured multiparametric data that was transmitted daily. Crucially, a workflow process was set up such that study investigators could typically contact patients less than a day after receiving an event alert and arrange any necessary follow-ups for less than a week later.

The study authors point out that, in the recent TRUECOIN meta-analysis, the IN-TIME approach was shown to be beneficial for patients with heart failure, since it provides early enough warning to potentially prevent deterioration in the patient's condition due to new onset atrial fibrillation, asymptomatic ventricular tachycardia, or other adverse events. It is this early appraisal – facilitated by efficient workflow processes, including multiparametric daily transmissions — that make the difference in the IN-TIME study, authors argue.

As the European cardiology community gathers for ESC 2018, it's an excellent time to re-examine existing evidence for clues we may have missed, alongside the latest breaking research. That's why it's time to look again at IN-TIME.

Half a century of Shimadzu Europa's innovations

Mass spectrometry and ever more…

As Shimadzu celebrates its 50th anniversary in Europe, our EH representative spoke with Stéphane Moreau, Manager of LC-MS & Life Sciences at the Marketing Europe/Analytical Business Unit of Shimadzu Europa GmbH, about today's and many more decades of exciting clinical developments.

EH: Mass spectrometry has been widely used in various fields, yet only recently entered medicine. For lab clinicians, the challenge is to understand this totally different, more chemistry-based technology, for which they are not yet trained. How does Shimadzu help with understanding, use and integration of mass spectrometry into their daily routine?

Stéphane Moreau: 'Liquid chromatography coupled with mass spectroscopy (LC-MS) or tandem mass spectrometry (LC-MS/MS), began to be introduced into medical labs at the beginning of the 2000s, often used to diagnose inborn errors in metabolism, from profiling amino acids in blood spots from neonates. However, the revolution in how mass spectrometry is used in the clinical lab really began in 2006 – in microbiology labs. Up till this, the identification of bacteria and diagnosis of infections were based on traditional methods reliant on culturing, or sensitive and time consuming techniques such as 16sRNA sequencing.

'Shimadzu's Koichi Tanaka, who was awarded the 2002 Nobel Prize for Chemistry for his demonstration of the possibility of applying laser technology to biological macromolecules, was behind the invention of MALDI-TOF mass spectrometry. This created, for the first time, a system that enabled the rapid identification of microorganisms from biological fluids and offer rapid and accurate diagnosis.

Nevertheless, mass spectrometry is complex, especially in terms of sample preparation and handling, which creates a barrier for clinical labs because they particularly like to automate this step to reduce workload and minimize operator error.

'To overcome those practical problems and ease clinical workflow, Shimadzu introduced in 2016 the CLAM-2000 LC-MS/MS, the Clinical Laboratory Automated sample preparation Module. The system is fully automated and simple to use, offering the first fully-integrated LC-MS/MS sample preparation system. Additionally, having understood how labs would want to use LC-MS, Shimadzu has deliberately kept the system flexible; it is not a "black-box".

'This means that labs can use commercial kits, transfer their existing LC-MS/MS methodology, or create new tests, all of which will be compatible with the automated system. In this way, the CLAM-2000 fits into laboratory workflow providing simplicity for novice users and the complete flexibility or "openness" demanded by an experienced operator.'

Which classical procedures can be replaced by LC-MS/MS?

'There's a long list of potential analytical applications for which the CLAM-2000 could be used but, typically today, commercial kits are available to analyze immunosuppression, vitamin D, anti-epileptics, antibiotics, steroids etc. There is also potential use in toxicology, which is difficult to bring into a routine lab because of the risk of a high number of false negatives and false positives, and also in forensics, where solid phase sample preparation is currently an obstacle to use on the system.

'Shimadzu has started its European Innovation Center (https://www.shimadzu.eu/euic) headquartered in Duisburg, Germany. The EUIC has a decentralized structure and combines academic-scientific know-how from universities with Shimadzu's technological expertise to even better respond to leading users' needs, and also to create new solutions for tomorrow. Currently, a new database of available compounds – over 2000 new compounds – has been created that will increase the similarity index and recognition confidence. New high speed LC-MS/MS is also being tested. The aim is to have a system that is not only for use in toxicology labs but also, thanks to CLAM-2000, can be used in Accident and Emergency (A&E) units, which need a 24/7 service for rapid diagnosis – currently not provided by toxicology labs.

This newly designed MALDI-TOF mass spectrometer is functionally simple but provides outstanding MS performance in a compact footprint.

nSMOL is currently targeted for biopharma scientists and research groups. Do you foresee its application in the clinical lab? If so, what kind of lab would typically use the nSMOL technique?

'nSMOL stands for nano-surface and molecular orientation limited proteolysis. This proprietary technology enables rapid and accurate measurement of large molecules such as monoclonal antibodies (mAbs) in the blood. Although originally aimed for use by biopharma companies and CROs, it was hospital labs that showed the most interest in the technique. Traditional methods for mAb detection based on immunoassay require a long lead time to create the capture antibodies, are expensive and present the risk of contamination and cross-reactivity. Therefore, nSMOL offers a rapid identification method and quantification of mAb blood levels by LC-MS, applicable to routine testing of many different pharmaceutical antibodies as the methodology is the same regardless of the mAb under investigation.

'This is of importance for doctors who are treating patients for diseases such as cancer with new mAb-based (biologic) drugs to monitor and assess therapeutic levels, something that is very difficult to do today. Shimadzu is actively working in this field to develop the practicality of the analytical technique.'

Shimadzu Corporation in Japan and others developed a blood test to predict the risk of developing Alzheimer's disease. The test is based on immuno-precipitation and mass spec. Can you tell us more about this?

'Measurement of the amount of amyloid beta-protein (Aβ) deposited in the brain is used to detect early changes in individuals because it suggests they are at risk for Alzheimer's disease (AD). Methods in existence today for detecting Aβ -protein, PET Scan or CSF sampling, are not compatible with large scale screening of populations, being too expensive and/or invasive.

'Mass spectrometry by MALDI-TOF has shown to be useful for screening new-borns for anomalies such as sickle cell disease etc. Therefore, as part of an international collaborative research team, Shimadzu has developed a highly sensitive blood test to detect Aβ-protein using immunoprecipitation and mass spectrometry (IP-MS).

'Used in large cohorts of patients from Australia and Japan, the method detected early onset disease with 90% accuracy, as published in Nature magazine earlier this year. Initially, this methodology will be used in screening for AD, but hopefully, with time, it can be adapted to help in drug development and therapeutic monitoring as part of the on-going challenge to alleviate the high disease burden.

In view of the analytical and measuring instruments division of Shimadzu Europa's 50th anniversary, can you point to what made Shimadzu Europe so successful for half a century?

'If you look at Shimadzu's various technologies in analytical instrumentation, there have been many "world's firsts" and awards underlining Shimadzu's approach to overcome technological borders and provide the markets with even better qualities and solutions. Today, many of these technologies and methods have become standards for various applications and industries.

'Looking back to just Shimadzu's instrument part I am specializing in, the introduction of MS to the microbiology lab has been revolutionary in the time saved to have rapid diagnosis from days to just a few hours. New faster MS technology will continue to create robust and cost-effective tests suitable for routine medical laboratory use.

'nSMOL is a nice technology to have, because it's a way to measure the new drugs, the macromolecules the pharmaceutical industry is now moving towards, away from small molecules.

'Also the constant search for new ways to implement modern healthcare will ensure that Shimadzu Europe continues its success. One example I can think of is microsampling, originally designed for use in small animals, this device is currently a research only technique, whereby small amounts of blood (µl) can be taken by the patient themselves and sent to the lab for LC-MS, rather than the patient going to the lab.

'Another area is Probe Electrospray Ionization/mass spectrometry (PESI-MS), a new MS technique being tested on biopsy samples, today patients may have to wait for an anxious few weeks for a result. With PESI-MS, validated in Japan and under investigation in hepatocellular cancer in a cohort of Italian patients, an answer can be obtained in just half an hour.

'All the time we are, of course, seeking to improve sampling and sampling techniques and to make our software as intuitive and user friendly as possible to ensure the continuous popularity and practicality of our product offering.'

In 1994, **Stéphane Moreau** obtained his diploma from INSA (Institut national des sciences appliquées de Rouen) in fine chemistry and engineering with a specialization in chemical process engineering. He then started his professional career in laboratory equipment distribution before he joined the brand new Shimadzu France subsidiary in 2002. Since then, he has held various positions to develop the MS range business. Since September 2013, he has been product manager for the MS range with Shimadzu Europa.

CLAM-2000 provides users with a seamless integration of automated sample preparation with LC-MS/MS to improve data quality, sample throughput, laboratory efficiency and safety.

Vital vitamin D testing

LC-MS outperforms immunoassays

In recent years, clinicians have increasingly focused on vitamin D deficiency. Studies show that previous reference values – particularly for Vitamin D_3 – were most probably set too high. Liquid chromatography with mass spectrometry (LC-MS) can help achieve more precise measurements of vitamin D levels than previously established immunoassay procedures, explains Dr Torsten Binscheck-Domass, formerly a pharmacologist and toxicologist at the joint laboratory of the Charité and the Vivantes Group in Berlin, and an expert in clinical mass spectrometry at Thermo Fisher Scientific. However, in its current shape this complex technology is not suitable for all laboratories.

Report: Daniela Zimmermann

Although the relevance of the threshold values remains controversial, there is agreement on one point: Vitamin D deficiency is associated with a range of clinical pictures, such as osteomalacia or respectively, rickets in children, as well as with increased susceptibility to infections. In the aged, a lack of vitamin D can also have severe consequences, as Binscheck-Domass explains: 'Studies are currently being carried out to examine a correlation between vitamin D deficiency in older patients and osteoporosis as well as a reduction in muscle strength, which leads to an increased risk of falls. For older patients, falls are complications that can have severe consequences, such as fractures, traumatic brain injuries and long-term hospitalisation, etcetera.'

UV-radiation from the sun is a natural remedy, but is often not enough. 'We recommend vitamin D screening for people with little exposure to sunlight, particularly for vitamin D_3,' he adds. Basically, everyone whose face, hands, and ideally also lower arms, are exposed to the sun for at least 30 minutes twice a week should absorb sufficient vitamin D_3 to also last them through longer periods without sunlight. However, deficiencies are documented for hospitalised patients, people in nursing homes and sometimes even for children and adolescents who spend little time outdoors. Vitamin D_2, which is mainly absorbed via nutrition – such as edible mushrooms – plays a slightly less important role.

LC-MS separates the wheat from the chaff

One problem with measuring vitamin D levels in the body is that the different intermediate products are often very similar and cannot be differentiated correctly with antibody-based tests such as immunoassays. Together with the comparatively low concentration of calcitriol – the biologically active form – this often leads to measurement values that have little significance, the expert points out. LC-MS has a big advantage here as it can separate the biologically inactive epimers from the molecule of the vitamin. Therefore, LC-MS-based diagnosis achieves significantly higher specificity.

Currently there are still hurdles which laboratories need to overcome when switching from immunoassays to LC-MS, Binscheck-Domass explains; this centres less around the associated costs – the acquisition requiring investments in the mid-six figure range, depending on the device – but rather the changes to the normal work flows: 'These are complicated devices and you need trained staff who can not only operate the equipment but also carry out evaluations.' Furthermore, some laboratories are deterred by regulatory requirements because the qualification of the systems requires a lot of effort, with numerous calibration and test runs.

Torsten Binscheck-Domass MD is a Systems Lead Scientist in Clinical Mass Spectrometry at Thermo Fisher Scientific. Qualified in medicine, he is a medical and forensic expert consultant in analytical pharmacology and toxicology. He has more than 25 years of experience in the fields of therapeutic drug monitoring, drugs of abuse testing and systematic toxicological analysis. Dr Binscheck-Domass is a strong advocate of clinically applied LC-MS/MS and has been exploring the technology's unique benefits to clinical labs for more than 10 years.

Selection criteria for a laboratory information system

Marry (a LIS) in haste, repent at leisure

Buying a laboratory information system (LIS) means entering a long-term relationship with a software vendor. The selection criteria are many, but which, ask Markus Neumann, Harald Maier and Gabriele Egert, are just fashionable and which might be underestimated?

The decision to buy a LIS – i.e. to form a relationship with one or more software vendors – is based on a slew of criteria, and excitement occurs over a long-term relationship. However, years pass before quality can be assessed.

Hard economic, technical and functional criteria can easily be expressed in figures, whilst others are 'soft' and difficult to quantify; however, they should provide sound information to shape quality in vendor/user cooperation. A purchasing decision results from balancing hard and soft factors.

Specifications

The basis of a specifications document to be provided to bidders for the tender is what's required. If there is no in-house IT specialist, use of an IT consulting firm might be advisable. The checklist offers an initial overview of topics to be covered. Vendors invited to submit a quotation need careful selection. Vendor criteria e.g. financial position, years of continuous market activity and responsibility/accountability.

Visits to reference labs and information exchange with users can offer important insights. Beware: although criteria are important, they are no guarantee that software development will continue.

Technical criteria

Hard data concern software, hardware and database structure. Which operating systems, programming languages and web technologies will be used? How does the database perform under heavy workload? An important question is user autonomy. Can you customise parameters, e.g. database queries? What training is included; what cost? Finally, physical interfaces support must be ascertained: Are popular interface protocols, e.g. HL7/IHE or ASTM, used and how are they practically integrated within the lab instruments? For vendors, programming customised device interfaces is a core business; over years this can amount to several thousand euros per analyser – a significant position in the budget.

Interfaces are also relevant in background processes, such as billing and controlling, or external communication with physicians to exchange order data and results.

Functional criteria

Every vendor offers many modules listed in the table under 'Functionality'. However, it makes sense to look at procedures and review their control by master data and parameters.

Nowadays, many lab workflows must meet certain standards. Quality management standards, or ISO 15189, 17025, or even ISO 22870 for POCT, are pretty obvious; others, such as GMP for blood donations, or for own blood donations, are less well known.

Generally, the trend is towards process monitoring. If a lab has standard operating procedures (SOPs) they can visualise the specific workflow of core processes to ensure relevant standards are met. Laboratorians should have easy access to quick visual overviews

Continued on page 20

Checklist for a LIS selection

	Feature	Explanation
Company	Size, financial position	Number of permanent and freelance staff, revenue, core business
	Continuity, accountability/responsibility	Type of company, year of incorporation, guarantees, ISO certification
	Reference customers	Number, size, scope, reputation
	Customer testimonials	Adherence to deadlines and delivery schedules, keeping promises, staff commitment, cooperation wi
	Soft skills	Personality and competence of vendor's staff during conversation
	Implementation concept	Is it comprehensible? Volume, solution visualisation
	Service	Hotline, response time, specialist availability
	Training	Documents, online support, on-site training, seminars
Product	Architecture	Client-server architecture, periphery, central master data server
	Hardware	Central computer, PC network, terminals, printers, storage space, operating system
	Software	Data base, data protection/privacy concept and confirmations, use of standard software, customisati
	Response time	Depending on database volume, number of web connections and online users (particularly in multi-s
	Maintenance contracts	Type and scope, hardware, software, remote access
	License policy	Online devices, database, multiple installations (campus license), pay-per-use (instead of purchase)
Functionality	Modules	Clinical chemistry, microbiology, blood bank, pathology, billing, order entry, automation and control
	Data protection/privacy concept	Permission-based, controlling access to patient data (e.g. lab values)
	Tracking	Search and sort functions, order status and sample tracking
	Compliance	RiLi-BÄK (in Germany), ISO 15189, ISO 17025, ISO 22870, GMP, etc.
	Master data management	Data maintenance, parameters, copying, use of legacy data, across modules
	Order entry and capturing results	Keyboard, card reader, order entry, material ID, different bar codes, device interfaces
	Quality control	RiLi-BÄK (Germany), Westgard, other quality systems, visualisation
	Technical and medical validation	Auto-validation, rules, alarms, automated repeat measurements, visualisation
	Reading	Sort criteria for orders and lab, rules systems, ICD codes, footnotes in identical texts
	Billing	Multi-client capability, service portfolio, accrued accounts
	Archiving	Procedure, duration, access, reactivation, archiving of image data
	Statistics	Saved and spontaneous queries, SQL assistant, export to standard software
Integration	Configurability	Adaptation of software and user screens to the on-site situation
	Internal communication	Link to HIS and departments/wards, POCT devices, de-central printers, standard interfaces can
	External communication	Link to other hospitals, specialist physician labs, lab groups
	hardware	Use of existing printers, scanners, PC, receipt readers
	Existing data	Use of legacy data, retaining identification logic
Results	Costs	Acquisition costs incl. commissioning, database, operating costs
	Own contributions	Which contributions are required (configuration, AP computer, preparation of hardware and se
	Costs over five-year period	These indicate whether a Europe-wide tender is required

Automation reduces human error

The expert emphasises that switching to the new technology is worth the effort. 'The fact that the LC-MS can measure both types of vitamin D, D_3 and D_2 simultaneously and separately in one single measurement is a considerable advantage. These values are adjusted for the epimers, delivering a clinically valid result.'

There is no need for extensive extraction, accumulation or derivatisation procedures that had to be manually carried out with earlier LC-MS procedures. This not only reduces the staffing requirements, but also the error rate. 'Humans mix up samples, or overlook things – machines do not. Moreover, every single manipulation, every individual analytical step is documented,' Binscheck-Domass points out. 'In other words, the traceability of the result is complete. In this respect, the principle is equal to that of a classic chemical analyser in a clinical laboratory.'

Manufacturer delivers IVD ready

The lack of standardisation for these procedures is creating some tension. In the USA, the systems need IVD certification, and in the EU this will also be required from 2022. Many clinical laboratories currently still work with open systems. For these laboratories the switch of the devices to IVD-conformity standards is almost impossible to implement on their own, Binscheck-Domass says. 'The EU guideline will force laboratories that work with these systems to change their procedures substantially.'

However, here the industry is delivering a possible solution. Companies such as Thermo Fisher Scientific offer solutions in which the technical system, as well as the assays, are already IVD-certified. This saves the laboratories lengthy test runs, which would otherwise be necessary for a qualification.

Cascadion SM Clinical Analyzer from Thermo Fischer Scientific

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th instrument manufacturers, LIS and HIS
on of parameters (by user)
site facilities)
be configured (HL7, IHE, LDT, ASTM)
rver), database license, training by in-house staff

Progress despite challenges and delays

En route towards digital pathology

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Report: Mark Nicholls

The benefits of digital pathology have been well-documented along with the need for significant capital investment. Yet, as some pathology networks are discovering, there can be ongoing challenges to bringing an integrated system into play.

Path Links – a single managed clinical pathology network operating across Lincolnshire in the east of England – and Nottingham University Hospitals in the UK sought to go down the digital route from 2013 and drew up a business plan which reflected where the department was at that point in time and future considerations.

David Clark, consultant pathologist with Path Links and Nottingham University Hospitals, explained to delegates at the Frontiers in Laboratory Medicine (FiLM) Congress 2018 in Birmingham (in January) how his organisation is working through the process towards implementation of digital pathology.

Although there have been delays in the process, Clark told delegates that he remains optimistic that significant progress will be made throughout 2018. In his presentation 'Digital pathology – from business case to full implementation', he outlined the vision and the reasons why Path Links and Nottingham University Hospitals decided that the digital route was the correct way to go.

Tackling a backlog of cases

The backdrop, he said, was of a mature pathology department with highly standardised work conditions, good IT, and bar coding in place. 'We were in a good position for digital pathology,' he said. 'So why was digital pathology good for us? In 2013 we could see the writing on the wall; the workload had been going up rapidly, and cases had gone up, but they were also generally more complex.'

Each whole time equivalent consultant pathologist was handling about 4,500 cases a year, but it was also an aging workforce with 62% of the pathologists over 55, with several nearing retirement.

The situation took a downturn in 2017 due to losing staff through maternity leave and long-term illness with a backlog of cases as the seven-day turnaround time of 80% dipped to a 10-day turnaround time of about 35%.

When the department began looking at producing the business case for digital pathology, he explained, there was insufficient consultant capacity, despite a generally lean workflow. However, the department engaged with the project and began looking to increase existing capacity through improved workflow.

Targets were to increase capacity by 10-15% and reduce waste, use digital pathology as being attractive to enhance recruitment and retention, shift to a digital focus, and improve quality.

Implementation started in April 2016 with the April-November period designated for installation, LIS integration and validation.

Diagnostic reporting began in November 2016 with two pathologists reporting 5,000 cases digitally with remote reporting coming into play in December 2017 with digital workstations being installed in the Cellular Pathology department at Nottingham University Hospital allowing Pathologists in Nottingham to report cases digitally directly into the Path Links LIS.

Dr David Clark is a consultant pathologist for Nottingham University Hospitals and Path Links (a pathology network across all five district general hospitals in Lincolnshire). A histopathologist, he is part of the team implementing the integrated Haematological Malignancy Diagnostic Service for East Midlands Cancer Network, and is also on the Path Links Digital Pathology steering group.

Takeover aids implementation

'Digital pathology works for routine diagnostic use and remote reporting but we realised that workflow redesign and integration with LIS reporting systems is critical in realising the full benefits,' Clark pointed out.

While he acknowledges there have been teething problems with the implementation process – delaying plans for a significant roll out – he remained confident of Path Links reinvigorating its digital pathology project and aiming to move enthusiastically forward towards full implementation.

That has been boosted by the takeover of digital pathology company Omnyx by Inspirata on January 31, 2018, and in the joint presentation at FiLM 2018, Mark Lloyd, executive vice president and founder of Inspirata, outlined the acquisition of Omnyx and the new opportunities it would give to what is traditionally a cancer diagnostics company.

'We are a nimble and quick company,' he said, 'There's a great deal of opportunity to move quickly in this field to provide value for pathologists, but we know that requires a deep understanding of what the pathologist needs.'

Path Links – which was formed in 2001 by the amalgamation of NHS pathology services in Boston, Grantham, Grimsby, Lincoln, and Scunthorpe and provides a wide range of diagnostic investigations and clinical services to hospitals and 186 GP practices – is now hoping to press ahead with full digital pathology implementation.

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Precision cardiov

New bio for CVD

A range of new biomarkers and diagnostics for precision cardiovascular medicine were outlined in a session at the British Cardiovascular Society annual conference held recently in Manchester. Speakers from King's British Heart Foundation Centre looked at how mass spectrometry allows clinicians to measure large numbers of proteins simultaneously, discussed a new biomarker for cardiac ischaemia that was discovered by a proteomics approach, highlighted a diagnostic structure-function atlas for titin mutations in inherited heart disease, and with first phase ejection fraction outlined a marker for LV diastolic dysfunction.

In his presentation 'A multi-omics approach to cardiovascular risk in the era of precision medicine,' Professor Manuel Mayr highlighted the advantages of mass spectrometry in measuring proteins.

Measuring a wide range of proteins and lipids

'Mass spectrometry allows us to measure a large number of proteins simultaneously and to apply this technique to longitudinal cohorts so that we can associate biomarker measurements with onset of disease or disease progression,' Mayr said. 'Basic measurements to evaluate cardiovascular risk have not changed that much but, by using mass spectrometry, we can now measure a wide range of proteins and lipid species.'

He suggested that the time is right to take advantage of mass spectrom-

Marry (a LIS) in haste, repent at leisure

Continued from page 19

of processes, e.g. on a process monitor.

Data protection is a major challenge. Many people with widely differing training and task levels can be involved in processes, so access to sensitive data in a central lab and at POCT sites must be clearly defined. Thus a detailed data security concept is an integral component of any LIS offer. One aspect to address is the use of legacy data, since a new LIS concept usually involves replacing an old system.

One stop shopping is no longer the guiding principle. For some functions, software is better sourced from a specialist, e.g. for document management and document control programs that simplify tasks for quality managers.

Economic criteria

Cost is among the easier factors to define. Even when the exact LIS implementation and operating costs cannot be specifically determined pre-installation, an estimate is possible and necessary since tenders with a €209,000 amount, spread over five-year period, must be published Europe-wide.

Costs to consider include licencing fees, e.g. for database or execution environment; for software implementation and customisation and for a support/maintenance contract; plus, obviously, for hardware, e.g. computers/printers. In this context, decide which services can be provided in-house, either by the lab or hospital, and which existing ones can be used. New purchasing can bring the opportunity to part with obsolete technology.

Software and hardware installation could be done by an in-house IT team; so could training during the implementation phase, again reducing costs. All staff needs training when an electronic order entry system is implemented; however, training could take thousands of hours, so only key users should be trained by the software firm.

Conclusion

Purchasing a new LIS is a huge challenge, but is also an opportunity to examine all processes, weed out inefficiencies and update tried and tested workflows. A good LIS vendor is a partner for life – in prosperity and adversity.

Contact: Markus Neumann: markus.neumann@labcore.de

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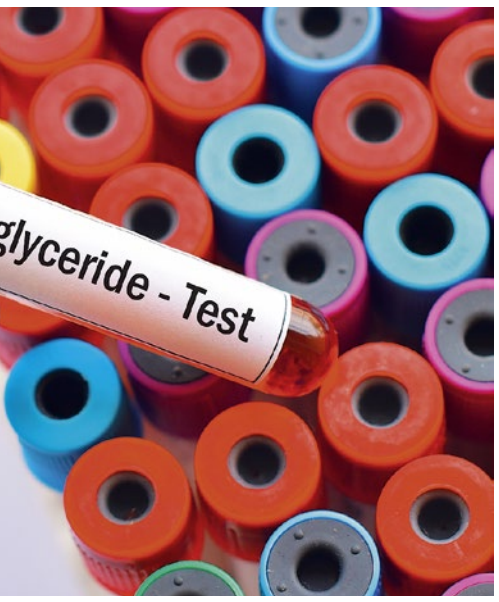


ascular medicine

omarkers

Manuel Mayr is British Heart Foundation Professor of Cardiovascular Proteomics at King's College London. He gained his medical degree at the Medical University of Innsbruck, Austria, and PhD in the University of London in 2005 for his thesis 'Cardiovascular Proteomics: Linking Proteomic and Metabolomic Changes'. He moved to KCL as Lecturer in the Cardiovascular Division in 2006 and by 2011 he achieved promotion to Professor. In 2013, he received the Outstanding Achievement Award by the European Society of Cardiology Council for Basic Cardiovascular Science.

etry profiling in clinical research and expand measurements from just monitoring total triglycerides, HDL and LDL cholesterol to deliver better cardiometabolic phenotypes of patients. 'Using mass spectrometry, we can simultaneously measure an unprecedented number of apolipoproteins in a single analysis rather than measuring ApoB-100 and Apo-A1 as surrogate for LDL and HDL cholesterol,' Mayr added.

In a recent study his group demonstrated that three VLDL-associated apolipoproteins, ApoE, Apo-CII and Apo-CIII, were associated with a higher risk of cardiovascular disease (CVD) and outperformed ApoB-100 in the Bruneck Study – a cohort with widespread use of statins.

He discussed in detail the benefits of measuring a panel of apolipoproteins by mass spectrometry and said that the strong associations of certain triglyceride species and VLDL-associated apolipoproteins with incident CVD support the concept of targeting triglyceride-rich lipoproteins to further reduce risk of CVD in the statin era.

'Currently, we just monitor lipid classes (total cholesterol, total triglycerides) as well as HDL and LDL cholesterol. The focus is on "quantity" rather than "molecular composition". Targeting certain triglycerides and triglyceride-rich lipoproteins can be a future strategy to reduce residual cardiovascular risk,' he pointed out.

Tissue-based proteomics approach

Mayr's research group has also set up a proteomics method to look for extracellular proteins in atherosclerotic plaques and highlighted the differences between plaques from symptomatic ad asymptomatic patients.

He noted that the inflammatory signature identified in symptomatic carotid endarterectomy samples could be measured in plasma. The plasma signature was not associated with early stages of atherosclerosis but was associated with progression of early atherosclerosis to advanced atherosclerosis and cardiovascular diseases.

'Inflammatory biomarkers identified by a multi-omics approach in human symptomatic atherosclerotic plaques predict progression of atherosclerosis to manifest CVD,' Mayr concluded.

Using a tissue-based proteomics approach to identify inflammatory plaque biomarkers could reveal novel companion diagnostics for anti-inflammatory and aggressive lipid lowering therapy. With a shift in risk factors and the advance of novel treatment strategies, there may be a need to expand on the current cardiovascular biomarkers.

In other presentations by speakers from King's College London, Professor Michael Marber discussed cardiac myosin binding protein C as a novel biomarker for cardiac ischaemia; Professor Matthias Gautel spoke about 'A diagnostic structure-function atlas for titin mutations in inherited heart disease', and Professor Philip Chowienczyk described 'First phase ejection fraction – a marker for LV diastolic dysfunction'. mn

Myths and truths about antibiotics, antiseptics and vaccination

Differentiate and select

Sixty-two percent of Germans fear antibiotic resistance, according to a survey recently conducted by the German Federal Institute for Risk Assessment. 'Patients colonised by multi-resistant pathogens are particularly scared. But many of these fears are rooted in misunderstandings,' explained Professor Mathias Pletz, Director of the Institute of Infection Medicine and Hospital Hygiene at University Hospital Jena, speaking at the Congress for Infectious Diseases and Tropical Medicine (KIT), held in Cologne, Germany, this June.

Many people believe the development of resistances can be avoided by the correct use of antibiotics. However, this is wrong: the development of resistance is part of bacterial evolution. Resistance can neither be predicted, nor avoided,' the KIT Congress President explained, adding: 'in permafrost soil, in bacteria that are more than 30,000 years old, the same resistance genes were found that we see today in vancomycin-resistant enterococci (VRE). It's true, however, that the spread of resistance genes and of multidrug-resistant organisms (MDROs), does correlate with the use of antibiotics: the higher the use of antibiotics, the faster the development of resistance.'

MDROs divide more slowly than sensitive bacteria

Another myth is the claim that MDR bacteria are in general more aggressive than sensitive bacteria. It is correct that MDROs, as a rule, divide more slowly than sensitive bacteria. Resistance genes offer a benefit only when antibiotics are present. If not, they are nothing but a genetic burden. In people who carry MDROs, this reduced biological fitness of the MDROs leads to the human flora being able to overwhelm the MDROs if no antibiotics are administered over a lengthy period of time.

'Increased mortality in the case of severe MDRO infections is mostly due to the fact that the initially administered antibiotics did not help because, in the early stages of an infection, the physician does not know which type of pathogen caused the infection and thus treats "on suspicion". Today, detection takes one to two days, which is exactly why we need faster diagnoses,' Pletz emphasised.

The fact that no new antibiotics are being developed is, above all, an economic issue, since their development can take up to ten years and can cost up to one billion US dollars. To make this investment volume economically feasible, Pletz and colleagues demand an extension of patent protection as in the USA. 'There is reason to hope, because recent literature describes many substances with antibacterial effects that have the potential for clinical development,' Pletz said, addressing another widespread misunderstanding.

It is equally misleading to describe MDROs as a mere hospital problem. Whilst, in Germany, MRSA is found mainly in hospitals and numbers are decreasing, other types of pathogens are gaining ground, such as multi-resistant gut bacteria, so-called ESBL-producing bacteria, which enter the body via food. In Germany, 10-13 per cent of patients admitted to a hospital are found to carry this pathogen; in India, 40-60 per cent of the general populace are colonised. They are not eradicated by antibiotic therapy – quite the contrary, further resistances are created.

The renowned infectiologist proposes a three-pronged approach to fight antibiotic resistance: 'The alpha and omega is a rational approach to antibiotics in line inter alia with the Antibiotic Stewardship Programme (ABS), which is tested and demanded in hospitals. Another important issue is proper hospital hygiene. It is the only way to effectively prevent MDRO transmission from one patient to another. Last and by no means least, there is vaccination, e.g. influenza and pneumococci vaccinations are effective measures to reduce the number of antibiotics prescriptions in the out-patient sector and thus to reduce the development of resistances.' Today, quality management of antibiotics prescriptions is well established down to the general hospital level. However, this does not solve the problem in the non-hospital sector where, indeed, 85% of all antibiotic prescriptions are generated, mostly with neither lab results nor X-rays (www.rai-projekt.de).

There are two possibilities to increase the safety of decisions for or against antibiotics: 'Either rapid diagnostic tests for biomarkers in the blood, to find out whether we are dealing with a viral or a bacterial infection. A study conducted in Hanover showed that, with such a rapid test, we would be able to reduce antibiotic prescriptions by general practitioners (GPs) by up to 60 percent. The second option is the direct detection of pathogens in a rapid test. Last winter we benefited immensely from an influenza rapid test done with a throat sample. This test detects viruses within 20 minutes and we used it right in the emergency room.'

However, as Pletz points out, many of these rapid tests are not reimbursed.

No antiseptics without indication

Another problem, which is almost as pervasive as antibiotic resistances, are hospital-acquired (HA) – called nosocomial – infections. The number of the six most important HA infections is twice the number of the 32 most relevant contagious diseases. Europe-wide, this translates into 2.6 million infections and approximately 90,000 deaths per year.

Infections caused by exogenous pathogens are easier to avoid than those caused by endogenous pathogens. 'In the past few years research has focused on antiseptics, since they can reduce endogenous bacteria. Since antiseptics don't kill microorganisms selectively, their use needs to be plausible and it needs to be part of hospital-wide hygiene plans and policies. Non-targeted use does carry certain risks and is to be avoided,' said Professor Simone Scheithauer, Vice President of the Congress and Head of Central Hospital Hygiene and Infectiology at University Hospital Göttingen, Germany.

The case of the central venous catheter (CVC) illustrates the benefits and limitations of antiseptics. 'Rather than using a fast alcoholic substance or a mixture of alcohol and PVP iodine to disinfect the entry on the skin, over the past few years a combination of alcohol and octenidine respectively chlorhexidine with remanent efficacy has become popular.

In 2015, Mimoz et al. published their results in The Lancet showing that the use of chlorhexidine significantly reduced catheter-induced sepsis,' Scheithauer explains. The German Commission for Hospital Hygiene and Infection Prevention (KRINKO) thus recommends the use of such combination products.

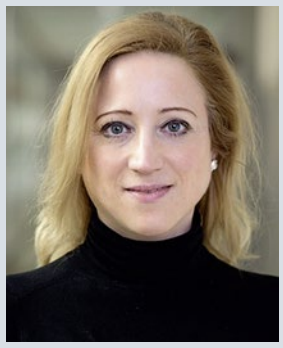
Antiseptic occlusive dressing

With particularly vulnerable patients, or when high infection rates are recorded, the commission at the Robert Koch Institute recommends antiseptic occlusive dressing for vascular access. 'When local antiseptic administration is effective it makes sense to apply the substance right at

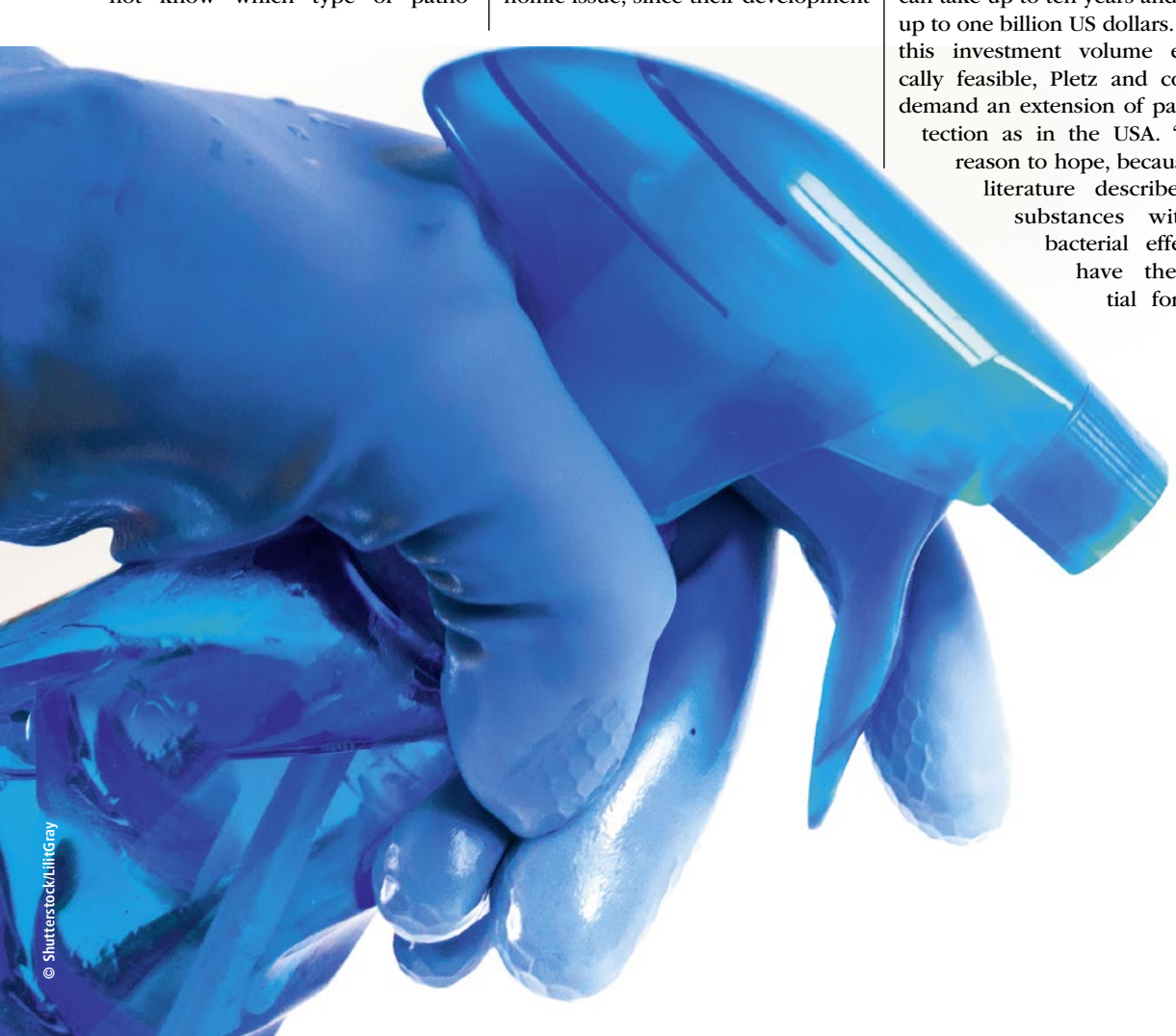
Antiseptics for external use with different degrees of efficacy: the range covers purely alcoholic (far right) and remnant solutions as well as impregnated occlusive dressings and skin washes (far left). Photo: B. Dinkloh

Professor Mathias Pletz MD specialises in internal medicine and pulmonology and is also certified in infectiology and hospital hygiene. He gained his medical degree in Leipzig, Germany, and then became a research fellow at Emory University's Rollins School of Public Health and at the Centers for Disease Control and Prevention in Atlanta, USA, for two years. In 2008, he received his habilitation and in 2011, he became Professor of Clinical Infectiology at Friedrich Schiller University Jena.

Having studied medicine in Münster and Mainz, **Professor Markus Knuf MD**, in 1997 completed his 5-year training as paediatrician at University Hospital Mainz, with a focus on infectiology, paediatric immunology and neuropaediatrics. From 2001-09 he was a consultant at the Mainz centre; he then became director of the paediatric clinic in Wiesbaden and was appointed chair of paediatric infectiology and interdisciplinary paediatric intensive medicine at the University of Mainz.



Professor Simone Scheithauer MD graduated in 2000. Seven years later she became a consultant in medical microbiology, virology and infectious disease epidemiology. She was appointed consultant for hygiene and environmental medicine in 2010 and, in 2012, became a consultant for infectious disease. From 2014 she has headed the division for infection control and infectious diseases at the University Hospital Göttingen, where she became a professor in 2015. Very recently a professorship has also been offered in Göttingen, Germany.



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the risk site, usually as impregnated occlusive dressing,' said Scheithauer. 'Even with low benchmarks, a significant reduction of venous catheter-associated infections was confirmed.'

Antiseptic wash should be the last resort. This additional measure requires an indication and the pros and cons have to be thoroughly considered. Increasing resistance towards these antiseptics might lead to these substances being ineffective with exactly those patients who would benefit most from them.

Vaccination offers individual and herd protection

Vaccination is meant to achieve different objectives depending on the vaccine: in addition to preventing an infectious disease with possible sequelae for the individual person, vaccination aims to build up herd protection, i.e. the protection of patient groups who cannot be vaccinated. Obviously, another objective is eradication of the pathogen. Vaccination can create a protection between generations. 'A typical example of herd protection in a family is the vaccination against pneumococci. These pathogens can cause pneumonia and sepsis and are particularly frequent among infants and older people. When infants and children are vaccinated, the serotypes disappear not only in vaccinated people, but also in in the older, non-vaccinated herd,' said Professor Markus Knuf, Medical Director of the Paediatric Clinic of Dr Horst Schmidt Clinics in Wiesbaden, Germany.

As far as 'flu is concerned, children are the linchpin of transmission. Relatively speaking, they contract influenza more frequently than adults because their immune system has not yet matured and because they haven't yet had sufficient contact with influenza. Children thus discharge a high number of viruses. Moreover, there are anatomical and behavioural factors that facilitate pathogen spread. If we manage influenza among the youngsters, this might reduce the number of cases in adults. However, there are no really effective vaccines for small children.

On the other hand, adults who are vaccinated can protect children who are too young to be vaccinated from pertussis. Protection has to be renewed every six to eight years. Today, pertussis is seen most frequently among teenagers. It is often misdiagnosed as chronic bronchitis and we increasingly see teenagers infect non-vaccinated infants. In very small children, pertussis is more severe and can be lethal.

Varicella, known as chickenpox, is often considered a harmless childhood disease. Indeed, before a vaccine was available, chickenpox mainly affected children. About five per cent of varicella cases are associated with complications, which translates into 35,000 cases alone in Germany per year.

Herpes zoster reactivates varicella and can thus be rightfully considered a sequela. 'About 50 percent of chickenpox patients also contract shingles. Thus, varicella vaccination not only aims to reduce varicella complications but also herpes zoster incidence. Adults can be protected from reactivation by a specific herpes zoster vaccine. A vaccine, however, that had been available for about ten years turned out to be insufficiently immunogenic,' Knuf pointed out. 'A new formula containing an adjuvant promises significantly better results.'

Climate change draws tropical pathogens to Central Europe

The Asian mosquito goes West

Report: Brigitte Dinkloh

Rising temperatures due to global warming are creating a permanent habitat in Europe for mosquitos from Asia. The Asian tiger mosquito (Aedes albopictus), or Aedes japonicas, are important vectors for the transmission of pathogens previously only found in tropical regions. However, at this point there is no reason to panic: the Asian tiger mosquito, when detected early on, can easily be eliminated.

Photo: Andreas Krüger, Editing: Klaus Jürries, ©BNITM

Asian tiger mosquito (Aedes albopictus),

No imminent danger from dengue fever foreseen

Professor Egbert Tannich, Chairman of the Board of Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany, sees no imminent danger of an outbreak of dengue fever or any other tropical disease. 'There are certain infections that are not imported by travellers – their source is in Europe. Cases of locally acquired dengue fever were reported in Greece and Croatia, several hundred cases of West Nile fever per year are seen in Eastern Europe, and there were several outbreaks of the Chikungunya virus in Italy and France in the past few years – with all of these the underlying cause is the change in mosquito population,' Tannich explains.

Our local, i.e. European mosquitos usually cannot be the vector for these viruses, but the warmer our climate gets, the higher the probability that the viruses can propagate in the new mosquitos. Permanent temperatures of more than 25°C are ideal for these pathogens to breed. The Asian tiger mosquito plays a key role in this scenario: globalisation over the past 30 years has carried it around the world. The mosquito eggs can survive for months in crevices of a tyre or in a plant container. Once disembarked, the larva hatches and the mosquito is on its way. That's how the mosquito came to Europe, with Genoa its first port of call.

Asian mosquitos hitched a ride over the alps

The Alps turned out not to be an insurmountable barrier for the Asian mosquito. Left to its own devices it can only travel about 300 miles per year, thus it simply hitchhiked a car or slipped onto a train to move up North. During the summer, Aedes albopictus has become quite a common guest in motorway rest areas and freight train terminals along the Upper Rhine. Some of these have even negotiated the congested German Autobahn A5 to visit Freiburg and Heidelberg.

The anti-mosquito strategy is successful - so far

'The good news is that we can eliminate the mosquitos, as long as they have not spread all over the place yet and have not yet formed large populations,' Professor Tannich says. So far, the anti-mosquito strategy has been successful, as Tinnich relates: 'We managed to eliminate the Asian tiger mosquito at all sites where we found it during a Germany-wide mosquito monitoring project covering the past three years. We destroyed their breeding grounds, such as vases or rainwater tanks. If we fail to take these measures early, the mosquitos will spread over central Europe the way they have already done in Italy, Spain and France. In Southern Europe, you can only try to reduce the population in order to prevent larger outbreaks of dengue and Chikungunya fever.'

The team at Bernhard Nocht Institute wants to find out more about the so-called vector or transmission competency of our local mosquitos. In Germany, there are about 50 mosquito species, in Europe about 200. 'We have high-security insectariums, where we offer Italian and German mosquitos a range of tropical viruses. After two weeks we check the climate chamber to see whether the viruses are present in the saliva. We found out that the Chikungunya virus, unlike other tropical viruses, can propagate well at 18 °C in the Asian tiger mosquito. Therefore,' Tannich explains, 'it's important to establish an early warning system to find and eliminate these mosquitos as quickly as possible to prevent a disease outbreak in Germany.'

Professor Egbert Tannich is a specialist in medical microbiology and Professor of Tropical Diseases at University Hospital Hamburg-Eppendorf, currently serves as Chairman of the Board of the Bernhard Nocht Institute for Tropical Medicine. He is also Director of the National Reference Centre for Tropical Pathogens. As Head of CuliFo, Tannich also coordinates a large multi-party mosquito research project in Germany.

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