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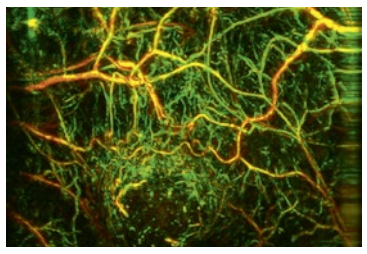
*RADIOLOGY* *10-16*

- **Psychoradiology: brain MRI-mining helps classify ADHD**
- **Optoacoustics: the sound of cells**
- **The DNA mismatch repair mechanism**

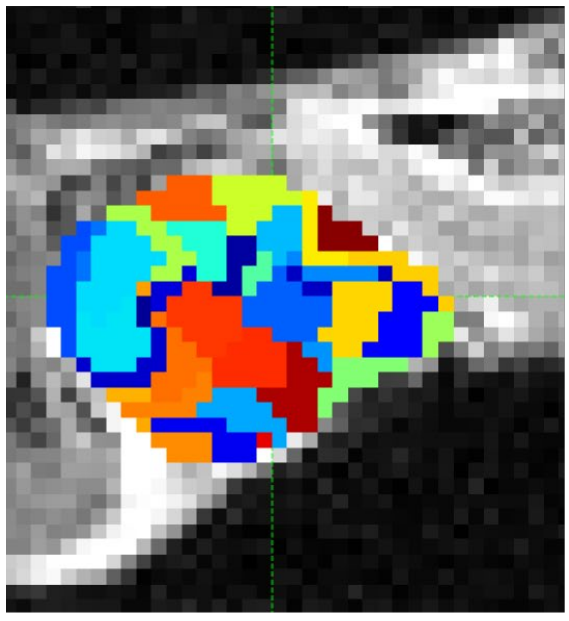


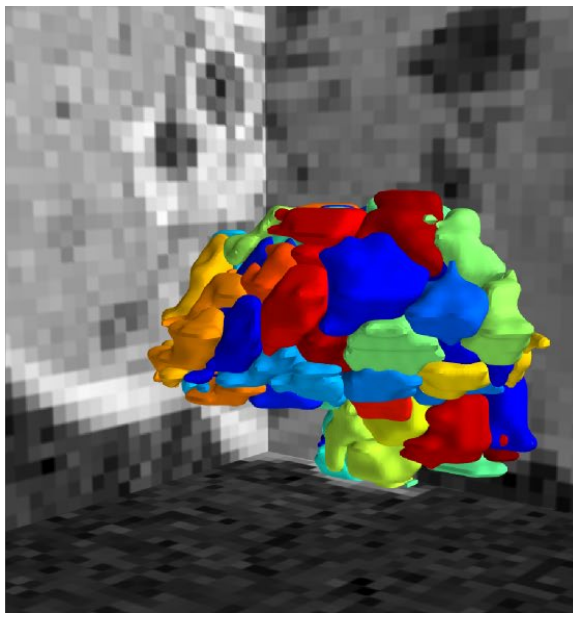
*IT & TELEMEDICINE* *20-21*

- **E-health developments in Spain**
- **Building an organisation's digital DNA**
- **The key to defeating cancer is knowledge dissemination**

# Machine learning is promising

**Machine learning is playing an increasing role in computer-aided diagnosis, and Big Data is beginning to penetrate oncological imaging. However, some time may pass before it truly impacts on clinical practice, according to leading UK-based German researcher Professor Julia Schnabel, who spoke during the last ESMRMB annual meeting, Mélisande Rouger reports**





**2-D view and 3-D volumetric rendering of contiguous perfusion-supervoxels for tumour parcellation defined on a 4-D dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) scan based on signal enhancement characteristics (Courtesy: Dr Ben Irving, ISMRM 2017)**

**Machine learning techniques** are starting to reach levels of human performance in challenging visual tasks. Tools such as the convolutional neural network (CNN or ConvNet), a class of deep neural networks that has been applied to analysing visual imagery, have become instrumental in segmentation tasks.

## Analysing such huge data is still a challenge

However, a number of obstacles remain before adequate image analysis arrives, starting with the huge amount of data analysts must work with, according to Professor Schnabel, computational imaging expert at King's College London. 'In imaging, the challenges are that we work in 3-D or 4-D, and we have a lot of features to deal with. If we're lucky, we deal with hundreds or thousands, but not millions of images, so we don't have a high number of image data to work with. We have this whole sample size problem.'

The professor also identified the high associated cost and imperfection of training data. Training data may be wrongly labelled, depending on the expertise of the observer. Furthermore, machine learning is resource-intensive: only specialists and consultants can perform special tasks. 'I personally couldn't distinguish a glass nodule from a semi-solid nodule. Only specialist consultants and expert radiologists can do that,' she pointed out. For a disease such as cancer, the image analysis team needs confirmation from pathology, which is often difficult to obtain.

For brain imaging, where different protocols exist, one sees different appearance of the same disease on different image protocols for the same patient and between patients. 'Disease location and size of these pathologies may vary quite significantly, and the appearance of disease may be very localised: it may be a very sharp "blob", or it may be very diffused or infiltrated,' she explained.

## Deep neural networks

The professor shared practical advice on how to work with CNNs appropriately. She stressed the size of the receptive field of a CNN will determine the amount of information that will be obtained. 'The size of patches used is important, since a large receptive field increases computation and memory requirements, and (max) pooling leads to loss of spatial information. In contrast , if you use very small patches, they are more susceptible to noise.'

As a solution, Schnabel points to using a multi-scale approach, i.e. having smaller patches operating on small filters and larger ones on larger filters, and putting them together in the end.

Oncological image analysis brings challenges of its own. Machine learning-based segmentation often degrades when deployed in clinical scenarios. This is caused by differences between training and test data due to variations in scanner hardware and scanner protocols and sequences, Schnabel explained. 'There is often an imbalance in the training or test data because of a different ratio of healthy vs. pathological cases, individual patient variability and individual disease variability – also within the same patient. For example, lesions in the liver usually are a secondary cancer, caused by a primary cancer elsewhere, such as in the colorectum.'

Therefore, it is crucial to choose the appropriate network architecture. Currently three models in literature are interesting: DeepMedic, FCN (in Deep Learning Toolkit) and U-Net, which owes its name to its 'U' shape. 'These networks use different approaches and for all these, there is the good, the bad and the ugly,' she pointed out.

## An ensemble of multiple models and architectures

All three networks use CNN based approaches with good performance, but there are a lot of meta-parameters – more than input cases –, and the architecture and configuration influence performance and behaviour. The ugly part is that chosen models and parameters may be suboptimal of other data and applications. 'Results and conclusions may therefore be strongly biased,' she said.

One solution could be to use an ensemble of networks; one such example is 'EMMA' (ensemble of multiple models & architectures), for which performance is insensitive to suboptimal configuration and behaviour is unbiased by architecture and configuration.

**Julia Schnabel PhD** joined King's College London, in the UK in July 2015 as Chair in Computational Imaging at the Division of Imaging Sciences & Biomedical Engineering, taking over the Directorship of the EPSRC Centre for Doctoral Training in Medical Imaging, which is jointly run by King's College London and Imperial College London. She is also Visiting Professor in Engineering Science, at the University of Oxford.

For segmentation in colorectal cancer with DCE MRI, Schnabel and team extracted variability of normalised signal intensity curves from the dataset using principal component analysis. 'It's a very simple technique. We just looked at the mean signal intensity of curves embedded within an over-segmentation approach, called superpixels

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*Tech firms, doctors and hospitals need greater cohesion*

# AI could enhance or disrupt healthcare

Report: Mark Nicholls

**Artificial intelligence (AI)** has enormous potential to revolutionise the delivery of healthcare, being able to remove the drudgery of routine tasks, join up fragmented care records, trigger alerts when abnormal results occur, speed-up the process of identifying clusters of patients by digging deep into electronic health records, and increase efficiency of healthcare staff resources. Yet to achieve its potential, there needs to be greater cohesion between digital technology companies, clinicians and hospitals if AI can enhance rather than disrupt healthcare in this early phase of its establishment, according to consultant cardiologist Dr Ameet Bakhai, deputy director of research at the Royal Free London NHS Foundation Trust.

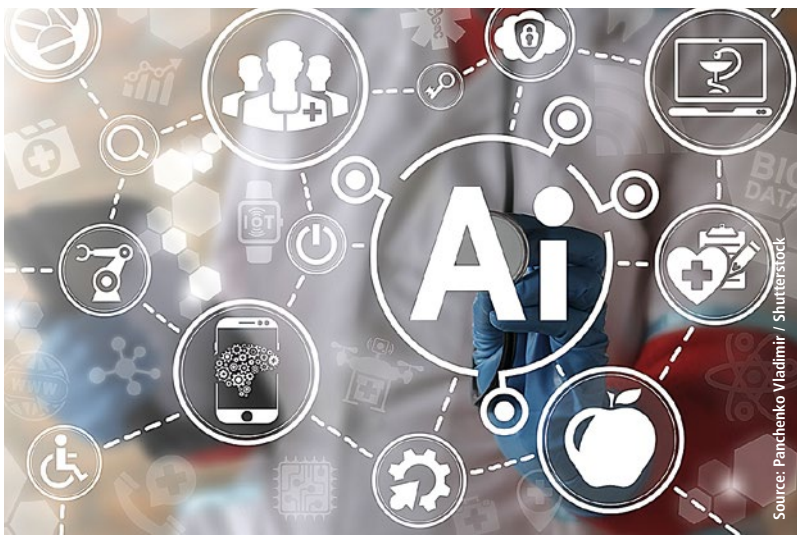
Speaking with European Hospital prior to his presentation 'AI in healthcare – delivery in diagnosis' at the UK Digital Healthcare Transformation Summit 2017 in London on 12-13 December, Bakhai explained that hospitals are at different stages of evolution in working with SMEs and large corporations in embracing digital technology and AI. 'Some are making small incremental changes, others are some years ahead and being innovative, while some are still in the traditional healthcare setting of the 1990s,' he pointed out. 'There are clinicians now willing to engage in trying out or helping to integrate a new technology; at the Royal Free Hospital we are blessed with key clinicians open to the role of digital technologies, such as remote monitoring companies, but across the NHS very few clinicians are doing that.'

Bakhai warned that the lack of a unified information share or strategy approach to how digital technologies as a group work with the NHS is an issue. Whereas the pharmaceutical sector has a strategy, with manufacturers aware of each other's technologies, and registering and publishing in advance their on-going clinical trials and seeking peer review early, digital technology companies tend to crowd the same space without a cohesive approach to broader development of AI and innovation.

AI is currently impacting on some areas, such as diabetes, self-management of epilepsy and rare kidney diseases. Other companies are interrogating databases to identify patients who meet certain criteria for a clinical trial, and some deliver software to track patients and ensure timely follow-up after procedures.

'They are removing the drudgery from some of things that we used to have to do manually, with more robustness and security,' Bakhai added. Also in development, he said, are companies creating disease specific avatars to help patients monitor and self-manage conditions – such as diabetes or heart failure – to remind them of appointments, scans, inform them about medication or their test results and to motivate patients to take exercise and their medications, for example.

While all at different stages of development and affordability, other companies use AI tools to gather data that will trigger clinical input when required, often earlier than patients recognise symptoms, thereby preventing unplanned hospitalisation, he pointed out. Other innovations support multidisciplinary teams across different centres to co-ordinate data and decisions and ensure these are relayed back to each hospital or centre, patients, GPs and social care teams.



Source: Panchenko Vladimir / Shutterstock

**Some innovations support multidisciplinary teams across different centres to co-ordinate data and decisions and ensure these are relayed back to each hospital or centre, plus the patients, GPs and social care teams**

However, the lack of joined-up working between the AI companies concerns the consultant, particularly with no generalised database of AI interventions existing, unlike pharmaceutical clinical trials. There is also no standardised consensus and guidance on measuring the impact of a clinical trial using AI technologies.

'Another aspect we don't know much about is how AI will disrupt the staff economy,' he observed. 'Will we be able to release staff from repetitive, low-impact work and reduce staff shortages in the NHS, and which staff are going to be impacted on most – doctors, nurses, healthcare professionals, pharmacists, managers or administrators?'

To ensure AI can fulfil its potential in a healthcare setting, Bakhai suggests a Faculty of Clinicians in Digital Healthcare or AI to support a more cohesive approach of these technologies in healthcare.

Touching on security, he said: 'We think we are less in a risk area with digital technology – but look at the impact of the recent Ransomware attacks in the NHS.' Ideally, he would like to see doctors, entrepreneurs, technologists, coders and others working more cohesively and for clinicians – while still active in clinical practice – working alongside digital technologies to conduct research and create an evidence base on the value of AI interventions.

'The way we measure AI value in healthcare is also going to be crucial,' he emphasised. 'Often, for digital technologies, we commission or introduce something with anecdotal or superficial evidence, hoping it will have some benefit, but we haven't really put them through the rigour that we'd use with any other intervention in healthcare.'

He concludes that if healthcare can work cohesively with technology firms and that they look ahead together regarding AI, he believes money will be saved and duplication reduced of competing companies in the same space. It could also help companies design and better evaluate the technology they offer and allow clinicians and hospitals to then be proactive, rather than reactive, in changing patient pathways.

Consultant cardiologist **Ameet Bakhai MD** is deputy director of research at the British Royal Free London NHS Foundation Trust, and is himself a cardiac researcher. He undertakes the design and management of clinical trials, health economic modelling and patient pathway innovations.
He is also a scientific advisor to NICE, health technology appraisal, pharmaceutical and device manufacturers and clinical trials organisations.

# A National Cen Healthcare Pho

**Construction has now begun of the National Centre for Healthcare Photonics in the UK to support companies developing technologies that use light for healthcare applications, Mark Nicholls reports**

**The Centre for** Process Innovation (CPI), a UK technology innovation provider for process manufacturing, is setting up a National Centre for Healthcare Photonics (NCHP) in a bid to extend the use of healthcare photonics technologies and make them more widely available for a range of applications, including the early diagnosis and monitoring of chronic diseases such as diabetes, eye problems, cancer or brain injury.

Scheduled to open in December 2018, the NCHP will be based in northeast England and provide open access facilities and expertise to help companies develop technologies and reduce barriers that commonly prevent early research and inventions reaching the market.

'Photonics is a key that enables technology for a range of healthcare products related to imaging, diagnostics and therapy,' Dr Tom Harvey, CPI's Strategic Programme Manager for Healthcare Photonics, pointed out. 'The new centre will provide expertise and facilities to help companies bring these products to market more quickly.'

The centre's intended scope of activity, he explained, covers an innovation space from the point where the key features of a new product or process have been shown to work in principle, to a point where the product has been tested and proven in the targeted end-use so that the technology is ready to become a commercial proposition. 'As such, the centre aims to be able to manufacture quantities required for clinical investigation and clinical validation trials but not to produce at commercial scale,' he added.

With an initial focus on imaging, diagnostics and therapy, the centre will provide a collaborative and flexible workspace for photonic technologies specialists.

Key facilities: a manufacturing area with controlled access, temperature and humidity control; flexible optics laboratories; a suite of life science laboratories for the preparation and analysis of samples; an electronics development laboratory; a workshop with facilities for rapid prototyping; an X-ray test and development lab; and a modelling and design laboratory with access to 3-D CAD design software, optics-design related software, image analysis software.

Alongside the infrastructure, equipment and accommodation, CPI will provide clients with services such as health economic modelling, clinical trial planning, understanding of the regulatory approval process, advice on CE-Marking, intellectual property protection, supply chain analysis and access to finance.

From a healthcare perspective, photonic-enabled diagnostic meth-

## Machine learning is promising

Continued from page 1

or supervoxels in 3-D. We then classified perfusion supervoxels in unseen cases using support vector machines to obtain tumour segmentations.'

This automated method was found to perform within the inter-rate agreement of two expert observers, but a correction step was needed when transferring the segmentation mask from the T2W to T1W DCE-MRI sequence, she noted.

### Gaining a more accurate tumour segmentation

'Tumours have considerable variation in shape, so we need to bring in some anatomical context and, to do so, we have developed a graphical representation of the neighbouring anatomy. We can improve segmentation by taking into account both local and global relationships; so we know where the bladder, lumen, etc. are, and build them into a pieces-of-parts model. By classifying these pieces of parts, we can reduce false positives and obtain a more accurate final tumour segmentation,' she explained.

Schnabel and team also performed segmentation inside the tumour using a technique called tumour parcellation, to extract locally meaningful, contiguous perfusion subregions from DCE-MRI scans. Ten female CBA mice with subcutaneously implanted CaNT tumours were scanned over eight days to monitor tumour growth and clustering of derived perfusion supervoxels.

Imaging casculature helped to look even deeper inside the tumour. 'We used 3-D fluorescence confocal microscopy, an imaging technique that has very anisotropic voxels of a few microns size. Endothelium and tumour cells were both fluorescently labelled, and approximately 60 slices where acquired in the z-direction. Vasculature was visible up to 30 slices from the surface.'

In lung cancer image analysis, most efforts concentrate on lung nodules or lymph node detection in lung CT. Deep learning is now largely replacing conventional CADe and CADx methods, which were based on texture analysis, handcrafted features and simple classification techniques. According to Schnabel, using deep learning, detection rate is generally very high and the main focus is now on false positives reduction.

### High dimensional multi-modality datasets are not big data

Machine learning is a promising tool in oncological imaging and image analysis, and the challenge is to find the right model parameters for good estimation and generalisation. 'We have high dimensional and multi-modality datasets, but it's not really big data, it's rather dense data. Cohort studies which collect large amounts of data ,' she added, 'will help a lot in that sense.'

*New UK centre will develop light technologies*

# tre for otonics

Eye examinations using photonics technologies can help to diagnose conditions early

ods are non-contact and can be done in-vivo or in-vitro, with or without additional probes, contrast agents or other types of marker.

'The aim is to help to improve the range and utility of photonic diagnostic methods available, with a focus on reducing the cost of manufacture of those devices so as to be able to address established market trends, such as the move away from hospital-based and delivered services towards more local or personal testing and diagnosis,' Harvey said. 'In general, the use of optical methods means less invasive and more accurate monitoring, diagnosis or location (imaging) of disease in the body.

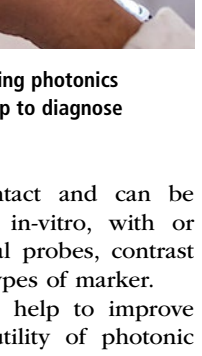
'In cancer diagnostics, differentiating between diseased and non-diseased tissues using non-contact optical imaging methods can be done in real time during laparoscopic surgery by illuminating the target area with a diagnostic probe beam which measures the Raman or infra-red spectrum of the tissue, or by exciting and imaging fluorescent probes that bind to selected target tissue types. Tissue classification can also be done by using time-resolved measurements of the spectrum.'

Other applications, Tom Harvey continued, include the opportunity to conduct skin cancer diagnosis without biopsy by using Optical Coherence Tomography and reflectance spectroscopy to image the suspect area on the skin; assessment of cardiovascular disease risk based on measurement of certain fluorescent proteins in the skin; and in vitro and in-situ diagnosis of bacterial infections in the lung providing rapid diagnosis.

In the United Kingdom, thermal imaging is already utilised to diagnose problems with blood circulation or to detect inflammation in thyroid eye disease and to classify burns, whilst a project for in-vivo, in-situ imaging of bacterial infections in the lung is at the clinical study phase.

Further innovations are expected, Harvey said, as resolution of imaging systems improve, the trend for miniaturisation of optical systems continues, laser power increases as costs fall and Light Emitting Diodes become more powerful and available with a wider range of emission wavelengths, further driving their adoption as a replacement to other light sources in medical use.

The United Kingdom's future National Centre for Photonics NCHP



**Tom Harvey PhD** is Strategic Programmes Manager responsible for Healthcare Photonics at the Centre for Process Innovation. His role aims to help companies with the translation of new photonic and printed electronic technologies into products and services for applications in Healthcare and Life Sciences. A Fellow of the Institute of Physics, he is an expert in these fields; before joining CPI he was employed in Industry for many years to develop displays, lenses, electronics and microfluidic components for a variety of uses.

*Inspired concepts increasingly impress global markets*

# Taipei hits highs in Medica 2017

**3-D visualisation, augmented reality, automated tumour classification – today, the Republic of China produces cutting-edge medical technology and it's a long time since 'Made in Taiwan' stood for inferior, copied products. Over recent years, this island state has successfully morphed into a productive and, above all, innovative manufacturer of medical technology available on the world market.**

Report: Wolfgang Behrends

**Taiwan presented its** most exciting products at this year's Medica trade fair in Germany – all bearing the prestigious national stamp 'Taiwan Excellence'. Organised by the semi-public Taiwan External Trade Development Council (TAITRA), Taiwan's presence at this prestigious show presented the cutting edge of Taiwan's medical technology.

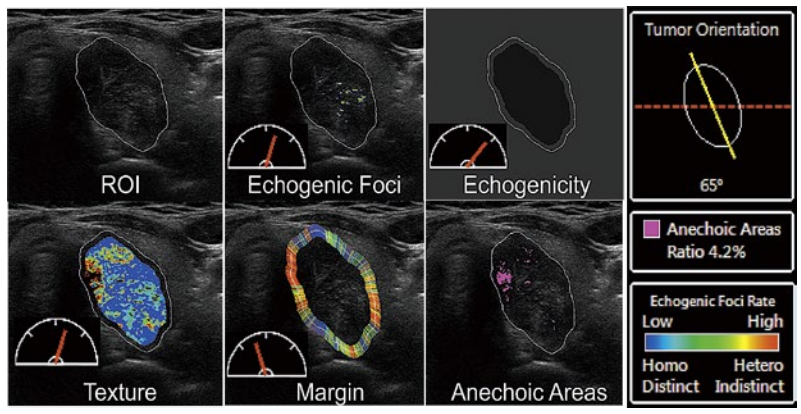
## An algorithm for how good and bad differ

Nowadays, artificial intelligence (AI) and deep learning are among the buzziest buzzwords in healthcare. Not surprisingly then that Taiwanese developers also explore the potential of these new technologies. For example, AmCad BioMed uses the power of algorithms to automatically classify thyroid tumours. 'Our software can analyse the characteristic features, such as microcalcification and echotexture, and calculate whether a tumour is benign or malignant', explains Peter Wu, President of AmCad. 'Using this method, we achieve an accuracy of 90 percent – on average, 15 to 25 percent higher than the capability of the best professionals.'

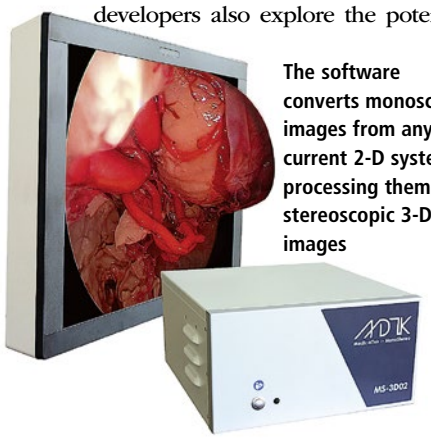
**Smart Surgical Glasses can speed up surgical procedures because the need to switch between patient and monitor is eliminated**

Machine learning enables software to improve its precision with each and every new case it analyses. 'Of course the doctor must make the final decisions', Wu emphasises, 'but, our software provides all the necessary information.' Increased precision is envisaged to reduce the number of unnecessary fine needle aspiration (FNA) biopsies by 50 percent and thyroidectomies by 30 percent.

The technology applied in another of the company's products works in a similar way: software automatically analyses airflow in the upper respiratory tract to determine the risk of Obstructive Sleep Apnoea (OSA) syndrome. 'This procedure normally takes several hours and requires the patient to stay in a sleep monitoring facility overnight,' Wu explains. 'Our system can do it in just 10 minutes, while the patient is awake.' Saving time and money by reducing length of hospital stay and the number of interventions is the professed aim of the product.
Contact: http://www.amcad.com.tw/en/




**AmCad BioMed software analyses tumour characteristics, such as microcalcification and echotexture, as well as its margins and anechoic areas**




**The software converts monoscopic images from any current 2-D system, processing them into stereoscopic 3-D images**

**Taitra's team at Medica 2017**


## Mixed Reality brings an unobstructed view without X-ray

Bridging the divide between the digital and real world is the vision of Taiwan Main Orthopaedic Biotechnology's Smart Surgical Glasses. The product is designed to enable the surgeon to look into the patient during surgery via Mixed Reality: X-ray images or tissue images of the regions of interest can be viewed in real-time and in full HD resolution (1080p). 'The relative position of the projected image to the patient is determined via four infra-red sensors,' Communications Manager Dr Min-Liang Wang explains. This provides the high degree of precision required in, for example, dorsal spinal surgery.

The developers are convinced that 'Smart surgical glasses will become a key tool for significant advances in surgery.' The fact that the surgeon does not have to switch between patient and monitor is said to reduce the duration of the procedure by 30 percent – a fact that also means less radiation exposure for clinical staff and patient alike. At this point, there is only a prototype of the smart operat-

*A varied portfolio: ultrasound, wound care, patient monitoring*

# All custom-built yet easy to use

**Konica Minolta constantly pursues new ideas and technologies for healthcare – which was clearly visible at Medica 2017, where the firm's novel products and systems were on show. Portable ultrasound, digital wound care or secure patient monitoring – the portfolio is highly diverse. However, the successful effort to balance customisation and intuitive usage was evident in all the solutions, Lena Petzold reports**

**After acquiring** Panasonic's Ultrasound Imaging Division, Konica Minolta entered the ultrasound market with Sonimage HS1, a portable system focused on point-of-care use. Randolf ten Cate, the firm's Marketing Manager for Europe, the Middle East & Africa (EMEA), explained: 'We developed the system for users who appreciate the added value of ultrasound imaging yet are not themselves radiologists, as is often the case, for example, in rehabilitation, anaesthesia or rheumatology.

'We also aim at users in intensive or trauma care who value portable, speedy solutions. The new ultrasound system is easily accessible and can be handled intuitively. It has only eight buttons, everything else can be entered via the touchscreen.'

Despite the ease of use, the system covers a great range of functions, including Colour, Pulse and Continuous wave Doppler, as well as linear, convex and phased array technology, for example.

'To keep the intuitiveness, we created a customisable interface where any user can add short-cuts to their favourite functions,' Marco Lagustena, EMEA Product Manager for ultrasound explains. Konica also focused on integrating powerful technology. 'Our goal was to obtain the quality of a cart-based system in a portable format so, for example, we included an 18 MHz transducer and Triad Tissue Harmonic Imaging,' ten Cate adds. The system takes almost no time to start, being ready to use in under 15 seconds. Battery-run, and operating for about one hour, when connected to a power-supply, or cart, it recharges yet remains operable. The system features two specific advantages Product Manager Lagustena explains. 'We include simple needle visualisation that works without any add-ons or additional hardware, and also we incorporated a special rheumatology function. The Rheumatoid Arthritis Work-flow, based on the DAS28 protocol, was programmed as a feature into the system, so users can follow it consecutively, experiencing a smooth workflow.'


**The Wounde Aide system automatically detects a wound's boundaries as well as the circumference and depth**

Following their key focus on easy usage, Konica Minolta branched into a different area to develop an innovative system that improves wound care management. 'With diabetes on the rise, there are more wounds to take care of and they are taking longer to heal. This obviously increases the cost of healthcare and the time patients spend in a hospital,' explains Zhang Qiu Ying, Head of Healthcare Innovation at the Konica Minolta Business Innovation Centre in Singapore.

## Capturing 3-D wound data

To minimise the time doctors need for the tedious business of documentation, Konica Minolta developed a device called 'WoundeAide', which allows clinicians to capture non-contact 3-D wound data. 'As of now, wound documentation is still mostly done manually and is not only rather inaccurate and time-consuming but often invasive and therefore painful for patients. Precious time is wasted by measuring the wound, estimating its depth, maybe photographing it and transferring the data to the hospital's record system afterwards,' Ying points out. 'Our intelligent system helps with documenting the wound more consistently and precisely within mere seconds.'

The system uses machine algorithms to automatically detect wound boundaries and it reduces the variability following manual assessments. Data is then automatically transferred to the hospital's record system where it can be stored, accessed and easily shared. Since no wound contact is needed, the risk of infection is lowered. Furthermore, trends may be identified from the gathered data. 'We want to enhance the system, so that in the future it will be able to make suggestions on how to treat a wound, based on the previously gathered input,' Ying says.

The system is on trial in several hospitals and nursing homes and the feedback is promising. 'We are working to bring the solution to Europe,' Ying reveals.


**The thermografic camera M16 Thermal detects temperatures ranging from -40 to 550°C**

## Thermal technology

Being a shareholder of Mobotix, Konica Minolta is also involved in security technology development, which could be relevant in healthcare, for example, as thermal technology systems, according to Sven Lessmann, Mobotix Business Development Manager for north

ing room (OR) glasses, but a market launch is planned for 2018 because the necessary clinical studies have progressed well.
Contact: http://www.surglasses.com/

### Extra-dimension out of the box

Technical innovations? Fair enough. However, they are of little value if hospitals do not have the necessary equipment to use them. This is where 'MonoStereo' by the 'Taiwan Excellence' winner MedicalTek comes in. This is a 3-D conversion box for endoscopes, as explained by Chairman Kai-Che (Jack) Liu. 'The software we developed converts the monoscopic images from any current 2-D system and processes them in real-time to stereoscopic 3-D images.'

A strong point in favour of the product is the high degree of compatibility. 'This is convenient for hospitals, because they already have all the necessary equipment,' he points out. 'Their endoscopy systems are simply connected to our conversion box. The depth is then perceived by the surgeon via polarised 3-D glasses.'

3-D endoscopic images not only improve visualisation of depth, they also flatten the learning curve. 'Surgeons need to convert the 2-D endoscopic images to 3-D movements in their mind. For some, this takes up to two years to get used to,' Liu explains. 'Our system takes this additional challenge away by adding depth to the images. This way, a surgeon only needs half an hour to get used to the endoscopic movement. Because it is a more natural way of perception, the added depth also results in more precision and therefore, better outcomes.' The conversion box does not impair the movement and zoom functionality of the endoscopes.
Contact: http://www.medicaltek.biz/

### Coming soon to a hospital near you?

While some of the 'Taiwan Excellence' products are as yet only in the prototype phase, others are already used in hospitals throughout Asia. Innovations such as the algorithm for tumour classification and the 3-D Conversion Box for endoscopes recently obtained FDA and CE clearance and thus will soon be admitted for use in USA and European hospitals.

Many Taiwanese companies are actively seeking sales partners – no doubt, after Medica, some contacts will be eager to knock on Taiwanese doors.

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**http://duesseldorf.taiwantrade.com**

**Sonimage HSI has only eight buttons; everything else can be entered via the touchscreen**

Germany. 'Thermal technology is used, for example, in early warning systems that are triggered when a critical temperature threshold is exceeded. Such a system, which uses cameras with integrated heat sensors, can detect infections in high-risk ICUs by identifying patients with fever.

'Another potential field of application is monitoring hospital equipment: increased heat emission is often a sign of imminent failure, for example if there is mechanical friction or when electrical components have a higher power consumption shortly before they break down. The system will detect and signal this unusual temperature increase early enough for maintenance work.'

Currently, thermal technology is being tested in a care facility in the Netherlands: a camera-controlled system warns the night watch staff of unexpected movement in patient rooms. 'This technology makes repeated night watch rounds obsolete', says Lessmann, adding that this 'increases flexibility and reduces pressure on the staff'. To ensure such a system respects patient privacy, Mobotix designed a particular configuration. 'All images recorded by the camera are pixelated. Only when the camera detects a potential emergency is the image recognisable and a signal is sent to the staff, who then check and decide whether an intervention is necessary.'

The initial feedback from a Dutch care facility is positive, above all ease of use and the practical help in daily routine are underlined. Thus the facility intends to expand the system. This seems to be another example where the approach 'easy to use but customisable' has borne fruit.

*Advertorial*

# Successful central patient monitoring

**Central alarm management of the Xenios console via the Philips IntelliVue MX800 patient monitoring system easily and efficiently achieves its goal through 'a combination of safety and innovation,' the manufacturer reports. 'The Barmherzige Brüder hospital in Regensburg and Xenios combine both in clinical practice.'**

**In clinical use** since 2014, the Xenios console combines three therapies on one platform for the benefit of the patient and support of the user. After three years in clinical use, the Xenios console has established itself. However, those, who move around in daily clinical practice will quickly realise that only everyday life defines the requirements and poses new challenges, which can best be met by working hand in hand with users.

Stephan Schroll MD PD, senior physician at the Barmherzige Brüder hospital in Regensburg, Germany, and Christian Hoff, clinical support Xenios AG, are long-standing partners, who know and trust each other. This is the starting point for expertise and safety as shown with our example.

The Barmherzige Brüder hospital in Regensburg has a modern intensive care unit with 28 beds, which include 20 ventilation beds. Due to the historically grown situation construction-wise, as well as the size of the intensive care unit, a central alarm registration is of great importance.

'This also includes central monitoring of the most important parameters when performing an extra-corporal membrane oxygenation (ECMO) procedure,' Stephan Scholl stresses. For this reason, a connection was installed between the Xenios console and the Philips IntelliVue MX800 central monitoring system. The connection can easily be established via the interface of the central patient monitoring system (Philips Intellibridge EC10 Module) to the data interface of the console (Xenios console, iLA activve system). This ensures central monitoring of the most important parameters, such as blood flow and speed of the pump in the extracorporeal circuit at all times.

Additionally, the most important pressure measurements are also centrally monitored in the ECMO system. By transferring the alarm settings of the Xenios console, no additional settings for central monitoring are necessary. All settings are made automatically after connecting the interconnection cable. This a clear advantage, says Dr Stephan Scholl. 'For us, the possibility of centrally monitoring important parameters of the ECMO systems means additional safety for the patients and, at the same time, a reduced workload in everyday life of the intensive care unit.'

That is exactly one of the goals of Xenios AG, the company explains: 'Safety in use and for the patient, bringing together innovation and support from experts for experts. From this, a continuous enhancement and progress results. In this concrete example, the alarm message is no longer optionally sent individually at the console in a room, but the messages are made accessible to the entire staff at a central point, for a whole team of therapists at the monitoring centre. 'We, in clinical support, listen to the uses and bring the therapists' experiences to our developers and the entire Xenios team,' Christian Hoff explains. 'Hand in hand; together into a secure future; for the benefit of patients and for their safety.'

**The Xenios console combines three therapies on one platform**

*Navigated ultrasound*

# The best intraoperative imaging technique

**New navigation imaging and neurophysiological stimulation techniques enable an approach to brain tumours long considered unresectable before and during surgery, but not one does it quite as well as ultrasound, according to a leading Spanish neurosurgeon.**

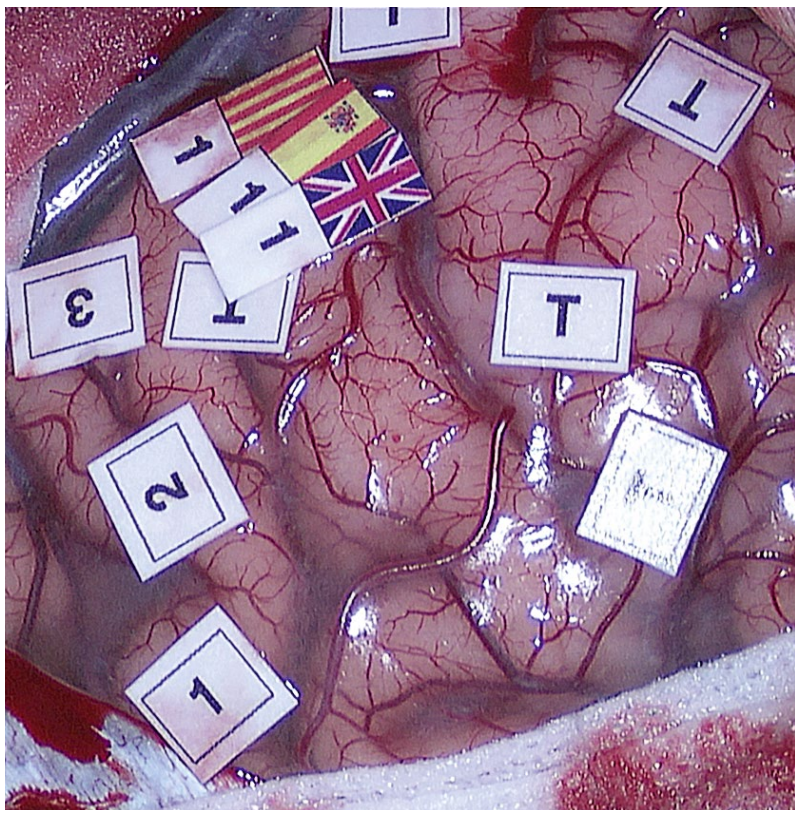
**Report: Méisande Rouger**

**Resecting an entire tumour** and determining brain shift remain challenging for surgeons in brain cancer surgery. However, they are likelier to overcome these difficulties if they use intraoperative ultrasound, according to Dr Cristian de Quintana Schmidt, neuro oncologist at Santa Creu i Sant Pau Hospital in Barcelona. 'Neuro navigated ultrasound provides the surgeon with confidence in the assessment of resection accuracy and in the determination of brain shift,' he said. Last August, during the World Congress of Neurosurgery in Istanbul, Turkey, de Quintana presented the results of a prospective two-year study on ultrasound use in intra-axial tumours. For surgeons, brain shift is a major problem. Even if they use pre surgical imaging to help plan surgery, the brain will change during the intervention; it will lose liquid and volume, shift shape and move, and ultimately make it harder for surgeons to perform.

## Intraoperative ultrasound takes just over two minutes

Unlike intraoperative magnetic resonance imaging (MRI), which requires 20-30 minutes time to adjust to pre-surgical images, it takes a little over two minutes (2 minutes 19 seconds) for intraoperative ultrasound to overlap with previous images.

Because ultrasound is so fast, it can be repeated as many times as necessary, enabling the surgeon to detect brain shift and evaluate how much tumour is left, almost instantly




**Awake brain surgery – Intraoperative image. Example of a patient monitoring three languages (Catalan as well as Spanish and English)**

'Ultrasound has changed the way we operate on patients. When I've finished a resection, I check if the tumour has been fully removed, or whether there is any residual there. In 14% of the cases, ultrasound helps to resect further, which significantly improves our results. Extensive resection tremendously increases patient survival and prognosis,' de Quintana pointed out.

Intraoperative imaging enables to safely excise tumours long thought to be unresectable. At Santa Creu i Sant Pau Hospital, ultrasound has helped de Quintana to successfully carry out surgery in 10-20 patients of the 40-50 patients he operates on annually.

Another benefit of ultrasound compared to other intraoperative techniques is that it is cheap and easily moveable across the hospital, without losing too much in image quality.

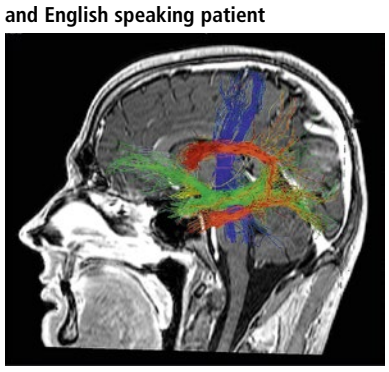
After studying hundreds of cases over two years, de Quintana observed that ultrasound had achieved 78% of correlation with pre-surgery MRI. 'That's a totally acceptable performance for intraoperative imaging,' he confirmed. Ultrasound is particularly helpful in visualising metastases, which are less infiltrative than glioma and usually easier to resect.

Last but not least, the learning curve is much faster than with MRI. 'All you need is a bit of experience. Ultrasound is not a complicated technique, but you need good equipment and good probes.'

All these benefits have convinced the researcher that ultrasound is the best imaging tool in his arsenal. 'Based on image quality, time, ease of use and cost, ultrasound is the most efficient intraoperative imaging technique at our disposal.'

Nevertheless de Quintana stressed the role of functional MR and tractography in the pre surgical setting. 'We are increasingly using these techniques to help prepare for surgery,' he said. 'They remain crucial to be able to localise tumour and determine our approach, in order to resect as much tumour as possible without damaging neurological function.'

**Tactography of a German and English speaking patient**



Tractography, in particular, is instrumental in visualising subcortical neural tracts and understanding how the tumour relates to surrounding structures. The technique relies on 3-D modelling based on data collected by diffusion-weighted images, and uses colour to image functions such as language, vision and motion. This information is then sent to the neuro navigator to facilitate surgery.

## Neurophysiological stimulation during surgery

De Quintana also highlighted the role of neurophysiological stimulation during surgery to help distinguish functional areas of the brain and evaluate patient response.

Brain mapping in tumours located in or close to key areas generating motion, vision and speech or linked to memory enables assessment of response while the patient is awake or asleep.

A surgeon, neurophysiologist and neuropsychologist usually perform this stage of treatment together. Once the patient is asleep, the medical team will gently wake him or her up to perform brain mapping and ask him/her to carry out tasks. Doctors then perform tumoural resection, and close up the patient when he/she is asleep or sedated.

**Cristian de Quintana Schmidt MD** is responsible of neuro-oncology in the department of surgery at Santa Creu i Sant Pau Hospital in Barcelona, Spain. He is a specialist in highly complex brain tumour resection and an expert in technological advances in this field. His publications, courses and conference presentations number more than a hundred.

*CyberKnife technology training in Brittany*

# Stereotactic radiotherapy spreads

**In Rennes, France, more than 850 patients have already been treated with a top accelerator equipped with a multileaf collimator, the first of its kind in the country, Mélisande Rouger reports**

**Brittany's capital Rennes** is leading stereotactic radiotherapy practice as Eugène Marquis Cancer Centre gears up to welcome worldwide technicians to train on the latest CyberKnife system, Accuray's powerful robotic radiosurgery system targeting small lesions.

The centre, based in the city's University Hospital (Centre Hospitalier Universitaire), is one of the few places in France to host the new CyberKnife M6 system, which features an adapted multileaf collimator in addition to IRIS or fixed collimator, an advance that decreases treatment time dramatically while allowing a very high level of precision. The system has helped treat patients with benign brain tumours but also colon, breast and lung metastases as well as primary tumours of the lung and liver ever since its introduction in Rennes in 2014.

Perhaps one of the most striking features of the voluminous machine, which has a 50-m2 footprint, is its millimetric precision in tumours smaller than 1cm up to 6 cm. Sessions with the CyberKnife last longer than conventional accelerators, but only one to five slots are necessary per patient. The technique used is hypofractioning, which consists in squeezing high radiation doses in the 8-24 Grayscale in as short as possible irradiation times. After each session, patients can go home and rest, therefore reducing the hospital stay.

This comfort and precision have enabled radiotherapy physicians to access tumours that were untreatable any other way than with chemotherapy or many radiotherapy sessions and to treat patients who were long regarded as inoperable.

'Stereotactic radiotherapy can help a lot of patients, especially those who are too fragile for surgery, or who have received a lot of chemotherapy. We've had very good results; it's a real technological advance. For us, it means another way of thinking and working in very targeted patients,' said Dr Elisabeth Le Prisé, Clinical Director of Eugène Marquis Centre.

The centre is equipped with four traditional accelerators and treats 2,200 patients annually. CyberKnife has also opened "a field of possibilities", especially in patients with colon cancer and resilient liver or lung metastases, according to Le Prisé. 'We can now give them a break from their chemo treatment and increase survival in a way that is comfortable for patients. That's something we had not been able to offer before.'



**The system reacts automatically to a patient moving**

Acquiring the system, and building the site to host it, was nothing easy and the medical team shed blood and tears to convince the administrators of the tool's value. 'I 've started discussions to acquire the system since 2008. Since we bought the CyberKnife we've increased our activity by 500 patients per year,' Le Prisé noted. $6 million was poured in by Brittany's Regional Health Agency (Agence régionale de santé de Bretagne) to build and fit in the platform. Equipment maintenance costs $365,000 annually.

Eugène Marquis is now a reference centre for Brittany and beyond. It will soon be a training centre for the rest of the world, after a partnership with Accuray is signed. Radiotherapy physicians, medical physicists and technicians will come from India, Eastern Europe and Africa to learn how to use the platform. Stereotactic radiation is one of the latest developments in radiotherapy, a field that has advanced hand in hand with radiology and IT.

*VR glasses could ease trauma of waking up in an ICU*

# A new therapy: virtual reality experiences

**Report: Madeleine van de Wouw**

**A patient walks** slowly into the Intensive Care Unit (ICU). He sits on a hospital bed, hears unfamiliar beeps and other sounds. Doctors and nurses arrive to talk about all the surrounding machines and how things work in an ICU. Everything is calm and without stress for the patient as he listens to them. Then the virtual reality (VR) glasses he is wearing are removed, and he returns to reality. The walkabout was a scenario. Its purpose was to deal with the traumatising effects of a sudden ICU admittance by having prior experience of being there.

Dr Michel van Genderen, an intern at Erasmus MC, works at the Franciscus Gasthuis & Vlietland in Rotterdam, The Netherlands, where, in November 2017, he initiated research into a method to help patients through Post Intensive Care Syndrome (PICS) by using VR. The project also includes Jolanda van der Wal, GZ-Psychologist at the same hospital, ICU specialists Evert-Jan Wils and Arjan Brouwers (Franciscus Gasthuis) and Jasper van Bommel (Erasmus MC).

## Why VR-Goggles?

'Many patients are unexpectedly hospitalised and put into a coma in the ICU,' van Genderen points out. 'When they regain consciousness, patients speak of a "hole" in their memories. They awaken in an unfamiliar surrounding with noises they don't recognise; they see people they don't know and are surrounded by equipment on which their basic existence depends. Besides that, the patient is unable to communicate, due to the use of a ventilator.

**Dr Elisabeth Le Prisé** has been head of the radiation department at Eugène Marquis Cancer Centre in Rennes, France, since 2000. She has also presided over the Eugène Marquis management team since 2011. A former hospital resident, she is an oncologist and radiation therapist specialising in cancer centre medicine.

'I've been working in this field for 30 years and, in the meantime, radiotherapy has taken a gigantic step ahead thanks to advances made in imaging and IT. The future will be MRI accelerators, and we would like to purchase one within the next three to four years,' the radiologist added.

For the time being, efforts should focus on improving software used for CyberKnife, she believes. 'Definitions of regions of interest and treatment planning are time consuming compared with other conventional accelerators.'

**Michel van Genderen and a patient testing the glasses that could help treat Post Intensive Care Syndrome**

Research shows that many of them suffer from post intensive care syndrome. They endure psychological problems, like anxieties, depression and returning nightmares. Physical complaints, such as fatigue and cognitive problems, like amnesia and concentration-problems also occur. These problems lead to a lower quality-of-life.

'We think that, when a patient experiences the ICU through Virtual Reality he will be able to deal with all things that occurred in a better way, because he learns how he got into the ICU and what all the beeps mean. Virtual Reality is already being used to prepare patients for upcoming treatment, but for this project we use this technique as treatment after an unexpected event. Naturally one can't prepare for such events.'

## Post-intensive care syndrome

'This is still relatively unknown and not much research has been done. The figures regarding the prevention of the Post Intensive Care Syndrome are not very reliable. International research shows that approximately 30 to 60 percent of ex-ICU patients have complaints. Research at the four hospitals in Rotterdam shows that 50 to 60 percent have serious issues.

'We put two-and-a-half years in preliminary research before starting with VR. Initially we needed financial resources. Luckily we received a fund of €45,000 from Stichting Coolsingel, which was used to develop the software.'

## Other trauma processing methods

'Sure, there are several forms like keeping a journal, reading brochures or watching information videos. This is not all very helpful to process the ICU treatment experience. A later visit to the ICU has shown to be more effective; however, that's almost impossible to organise. With Cognitive Processing Therapy (CPT) and Eye-Movement Desensitisation and Reprocessing (EMDR) you are completely reliant on your own memory and associations, which are not there for these patients.

'Using Virtual Reality is less dependent on memories and this may have a positive impact on patients. Many ex-patients have remarked that they feel out of control and would like to be able to experience the ICU again, with the explanation and context. VR might give them back control.'

## The research project

This involves 50 patients at the Franciscus Gasthuis who were admitted to the intensive care unit (ICU) with sepsis (blood infection). On the fourth day after they are moved out of the ICU into a 16-bed ward, which provides five VR glasses, the patients can request the use of VR-glasses for one week.

They are randomly divided into two groups: 25 patients see images of the ICU. 25 are the 'control' group and the images they see are of relaxing surrounding, such as a forest, concert or other soothing scene or event. All patients receive the same personal guidance.

**Michel Egide van Genderen MD** joined the ICU at Erasmus MC, Rotterdam, The Netherlands, in 2015, the same year in which he concluded his PhD. In 2016 he became an intern. In 2019 he will advance his training to become an intensivist. For his research, he aims to limit the impact of ICU re-admittance, and later to expand this understanding for other patient groups. He also wants to improve quality of care by training doctors and medical specialists to work with the technology he is using.

## Research results

'We expect to have results by mid-2018. If the results are positive, we can start to implement the method in other hospitals. We want to do this regionally, in cooperation with and from the Erasmus MC. Most important is that we can help patients.

'The fact that it is very effective was shown with our first test patient, José Smit, aged 63. She developed psychological problems after being committed to the ICU. After the treatment with the VR-exposure therapy she responded to have had a lot of help from it. She now sleeps and functions better. In the end, potentially it will reduce costs because patients will suffer less trauma. And there is the issue of the costs: aftercare will be less expensive.

'Initially the hospitals must invest in this technology but, down the line, it's also cost reductive for them. This research project might be a difficult path for patients – but not as difficult as experiencing the trauma – and the potential outcome is big. If the research results show that VR can be used as a preventive means, the gain will be even larger. In a couple of years, this may become mainstream.'

*The nurse's role in endoscopic procedures*

# Endoscopy education increases

**Hygiene is still a leading topic in endoscopy, and education remains crucial in Europe, according to Ulrike Beilenhoff, scientific secretary of the European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA). The two subjects took centre stage during the 21st ESGENA Conference, held during UEG Week in Barcelona this October, Mélisande Rouger reports**

**With around 600 participants,** lectures, posters, hands-on training workshops and industry symposia, all stressing the importance of multidisciplinary cooperation and all with good feedback, Ulrike Beilenhoff, scientific secretary of the European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA) was pleased with the three-day event. 'The Spanish Society of Endoscopy Nurses and Associates (AEEED) and Spanish Society of Digestive Disease Nurses (AEEPD) hosted the event – we have an excellent relationship with these two organisations,' she said.

From 1989, nurse **Ulrike Beilenhoff** has specialised in endoscopy since 1989 and was head nurse in an endoscopy department for more than 15 years. She now teaches endoscopy during nurse training in Germany. A founding member of ESGENA, Beilenhoff has served on its governing board for several years, and currently she is the organisation's scientific secretary, President of the Germany society of Endoscopy Nurses and editor-in-chief of the German journal Endo-Praxis.

## Highlights

Hygiene, advanced roles and education in different countries were among the most discussed aspects. 'The session on liver transplantation was also very important, because the endoscopy team handles complications if something goes wrong following surgery. In endoscopy, nurses have a very close relationship with the endoscopist.'

## Leading topics

'Hygiene has been a big issue since the early 2000s,' Beilenhoff points out, referring to the increased rate of multidrug resistant infections internationally. 'In the last three or four years a number of these infections have been reported in endoscopy. Examinations are more invasive, and there's a potential higher risk of infection. Infections highlight the important impact of staff training, appropriate reprocessing and quality assurance.

'Nurses' advanced role is also a major topic. Nurses already fulfil advanced roles in nutrition, functional tests and caring for special patient groups e.g. IBD patients. Only five European countries allow nurses to perform colonoscopy screening: the UK, Ireland, Denmark, Sweden and the Netherlands. Due to different national health systems and national laws, other European countries forbid this at the moment.'

'However, studies have shown that, to carry out these examinations, nurses are at least as good as doctors. In the UK, nursing and medical endoscopists have the same education. In Denmark, the Netherlands and Sweden, nurses receive a formal, officially recognised training to perform endoscopy examinations.'

## Endoscopy training for nurses

'After basic nurse training, which lasts three years, nurses should do specialist endoscopy training. In many European countries such as the UK, Ireland, Sweden, Italy and France, specialist nurses' education in endoscopy or gastroenterology is established at university level, as part of a bachelor or masters' program.

'In other countries, higher education institutions offer specialist training in endoscopy. A pretty current model across Europe is for nurses to receive gastroenterology and endoscopy education for one year, while they are working in parallel. This is not the case in Germany, where specialist endoscopy education for nurses stretches over two years.'

## Trends in Europe

'There is a clear trend towards university training, although nurses still train at school for basic and specialised education in many countries. But the trend is for countries to switch to university training.

'Additional training, for instance in hygiene or sedation, is delivered on the job.'

## New endoscopy techniques with clinical impact

'We now carry out a lot of procedures that replace surgery. Minimally invasive treatments have multiplied over the years. The endoscopist now does a lot of advanced endoscopic procedures, for instance tumour resection in the gastrointestinal tract, if the tumour is inside the lumen.

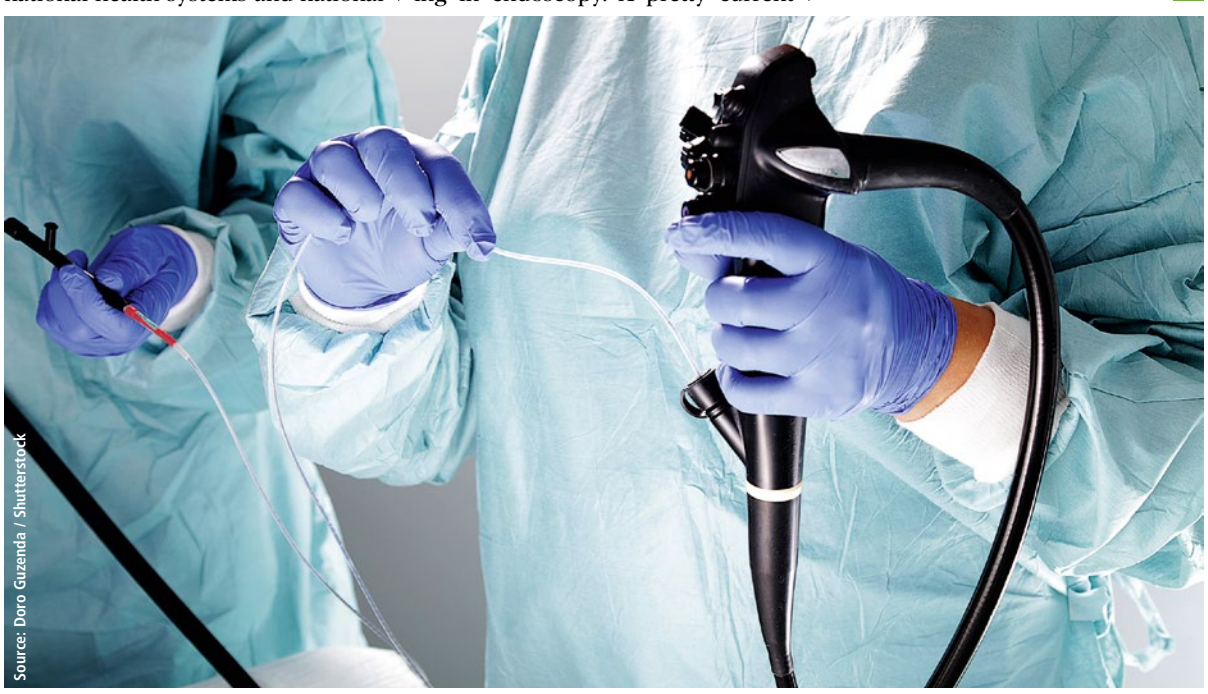
'Since nurses play an active role during a procedure,' Bellenhoff continued, 'new developments also influence their daily work, because deeper knowledge and new training skills are necessary.'

## Challenges

'We have two main tasks in endoscopy nursing: assisting the endoscopist during the procedure and specialised patient care before, during and after the procedure. In Germany and some other European countries, nurses are specially trained to administrate sedation of the patient. For sedation, you need to have a certain amount of experience to handle the medications, and you need to be aware of all resuscitation techniques, so you need special training.

'When assisting the endoscopist, you need a lot of medical knowledge because you look at the screen or at an X-ray study; you manipulate endoscopic accessories and play an active part during the procedure. So you have to understand what you are doing together.

'These are two totally different but fascinating tasks.'



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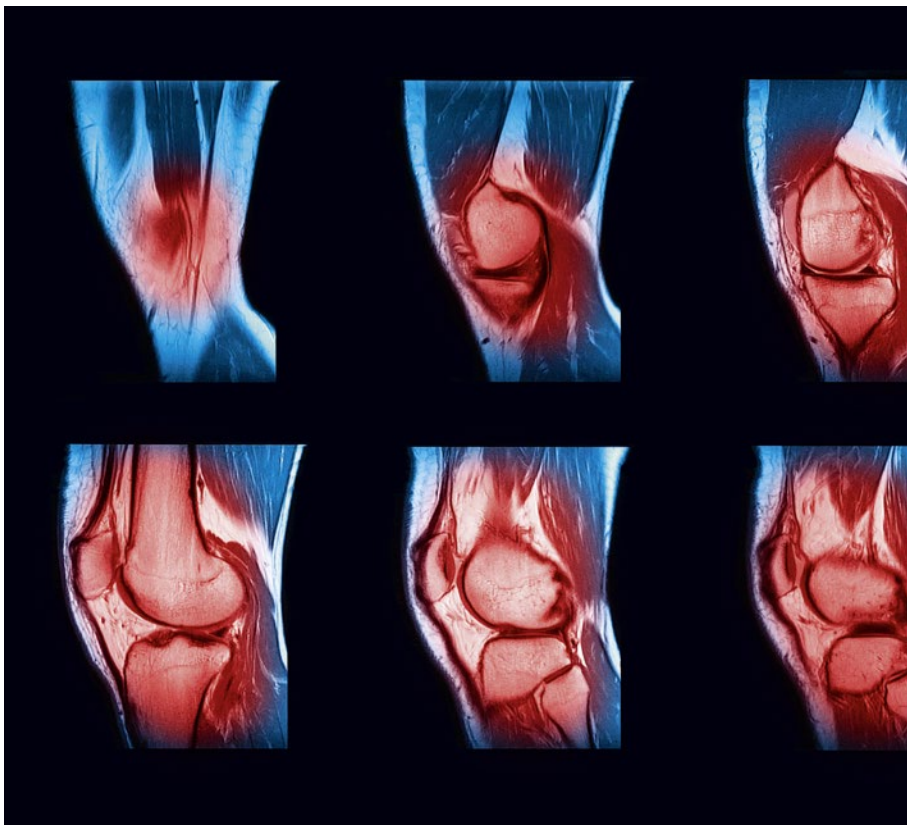


# Challenges in septic bone s

**Report: Beate Wagner**

**Infections associated** with osteosynthesis and prostheses are not to be underestimated: the infection rate is reported to be one to three percent after joint prosthetic surgery and five to 10 percent after osteosyntheses. 'When you include later infections, the rate is twice as high,' says Professor Andrej Trampuz, infectologist and Head of the Centre for Septic Surgery at the Centre of Musculoskeletal Surgery (CMSC) in Charité, Berlin, Germany. Since the avascular tissue of the implants impairs phagocytes, he points out, 'A mere 200 bacteria are sufficient to form a resistant biofilm.'

Biofilms that are a maximum of four to six weeks old are usually caused by highly virulent microbes, such as Staphylococcus aureus, Streptococci or Gram-negative rods that can be easily eradicated without replacement of the implant. By contrast, mature biofilms form low-virulent microbes, such as Staphylococcus epidermidis and Cutibacterium acnes. 'The older the biofilm, the more difficult pathogen eradication becomes and the more urgent is an implant replacement,' Trampuz explains.

Sequestrectomy and removal of infected bone material require aggressive debridement, local soft tissue and bone conditioning, one and two-stage exchange as well as post-surgery antibiosis. Efficiency of the antibiotic therapy is closely related to effective debridement and the reduction of pathogen load during surgery. The antibiotics should be bactericidal and biofilm-active and offer good bone penetration and oral bioavailability, such as rifampicin, ciprofloxacin, penicillin, amoxicillin, fosfomycin and gentamicin.

'We are currently witnessing a renaissance of local antibiotics therapy,' Trampuz says. 'Gentamicin and vancomycin can be applied locally in bone cement in a much higher concentration.' Prophylaxis requires 0.5 to 1.0 g antibiotic per 40 g cement. In the spacer, a dose of 2.0 to 4.0 g per 40 g cement is used.

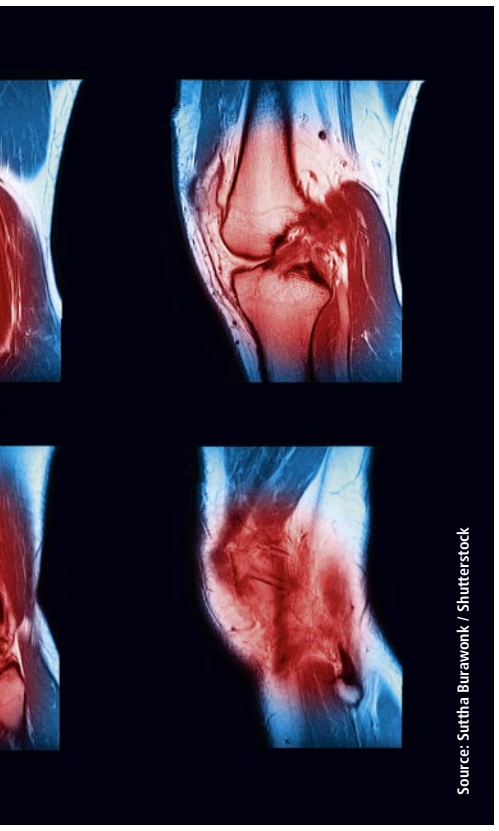
Professor Ingo Marzi of the Clinic for Trauma Surgery, Hand Surgery and Restorative Surgery at the University of Frankfurt, Germany, adds: 'Soft tissue coverage is of crucial importance in the therapy of osteosynthesis infections. Secondary reconstruction is most successful in a clean and properly vascularised bone and soft tissue bed.'

Reconstruction entails thorough removal of infected bone material and insufficiently perfused soft tissue, stabilisation of the limb with spacers, surgical closure of the defect with grafts or flap surgery and bone build-up of the impaired bone.

Marzi recommends the Masquelet technique for bone defect manage-

**Professor Marzi (middle) at the German Congress for Orthopaedics and Trauma Surgery**

*Infection – defect – regeneration*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# urgery

ment. In this, following thorough bone debridement and soft tissue coverage an antibiotic-loaded bone cement spacer is inserted into the bone defect. In a second intervention, the cement spacer is removed, without damaging the membrane, and the bone defect is filled with a mixture of BMP-7, tricalcium phosphate and endogenous bone. Bone tissue is harvested either from the iliac crest or via RIA technique (Reamer-Irrigator-Aspirator). 'Compared with other bone reconstruction methods the Masquelet technique is rather quick, even with large diaphyseal and metaphyseal femur or tibia defects,' Marzi says.

Unlike Masquelet himself, who did not apply antibiotics in order to avoid infection masking, Professor Gerhard Schmidmaier of the German University of Heidelberg uses the procedure to deliver bone cement and high doses of gentamicin and vancomycin.

One advantage is improved perfusion: 'It's amazing that today we


**Joint infections are not to be underestimated**

can improve bone perfusion with the help of the Masquelet technique,' says the interim director of Heidelberg's Clinic of Orthopaedics and Trauma Surgery. Today, due to periosteum induction bone defects of 20-25 cm heal well. 'In addition, locally applied high doses of antibiotics ensure that all bacteria are eradicated,' Schmidmaier points out. 'Masquelet used his technique solely for membrane induction and enhancement of perfusion, not to treat infections.'

Prior to the intervention cement is prepared in a bowl. 'This makes the cement a bit more porous and the antibiotic is released better,' Schmidmaier explains.

Nonetheless, he also routinely works with ready-to-use products such as Copa G+V, for example in infected pseudarthrosis. 'Bone cement loaded with a mixture of gentamicin and vancomycin,' he explains, 'catches up to 80 percent of all microbes.'

He recommends that, when placing the bone cement, it makes sense to create irregularly shaped edges on the bone, 'for the subsequent integration of the new bone, the bone cement should overlap onto the healthy bone material'. When the bone cement is removed after six to eight weeks, the objective is to spare the membrane.

For harvesting graft material Schmidmaier favours RIA, a procedure that allows acquisition of large volumes (20-75 ml) of high-quality autologous bone tissue. 'Research indicates,' he points out that morbidity decreases with harvesting using the RIA technique.'

In conclusion, he says: 'The Masquelet technique is suited for interventions with plates and nails but also in recent trauma. It makes sense from a biological point of view and the combination of gentamicin and vancomycin offers benefits. If a tissue sample is loaded with bacteria that do not respond to the antibiotics, the spacer can be replaced or a suitable antibiotic can be applied locally.'

*Old technique + new technology diagnose disease*

# Optoacoustics: the sound of cells

Report: Anja Behringer

**For centuries,** hands, eyes and ears were the physicians' most important instruments when it came to detecting and diagnosing disease. Today, one of the traditional techniques, percussion, is being revived, supported by state-of-the-art technology and dressed in a new name: optoacoustics.

In one of the most exciting visionary ideas in modern healthcare short laser pulses (optics) are transmitted to tissue where they generate ultrasound signals (acoustics) that allow the identification of cells and diseases in the body. The advantages of this technology? No ionised radiation, no invasive procedure.

Pioneer of clinical optoacoustics is Professor Vasilis Ntziachristos, Chair for Biological Imaging at the Technical University Munich (TUM), Germany, and Director of the Institute of Biological and Medical Imaging (IBMI) at Helmholtz Zentrum, Munich. His groundbreaking research not only sparks hope for cancer patients but also opens new diagnostic perspectives for Alzheimer's, diabetes and dermatological diseases.

## Multi-spectral optoacoustic tomography (MSOT)

The laser pulses penetrate the body where they are absorbed differently, depending on their wavelength and on the type of target tissue. These laser pulses create a minute rise in temperature which expands the tissue. Those equally minute movements generate acoustic signals – with each type of tissue producing unique signals. A blood cell for example "sounds" very different from a skin cell.

Ultrasound detectors on the skin surface register these different signals and a computer generates the corresponding 3-D image. Thus, single cells, for example cancer cells, can be detected. This is a major advantage compared to ultrasound, which cannot differentiate on this level, Ntziachristos explains. Currently, multi-spectral optoacoustic tomography shows its potential particularly well in aggressive melanoma cells. But their unique sound also gives away other cell types, which might allow surgeons to check accurately during a tumour resection whether indeed all cancer cells were removed.

Following successful animal studies the procedure is now being tested in human volunteers. Different clinical studies are currently being conducted for breast and thyroid cancer and peripheral atherosclerosis.

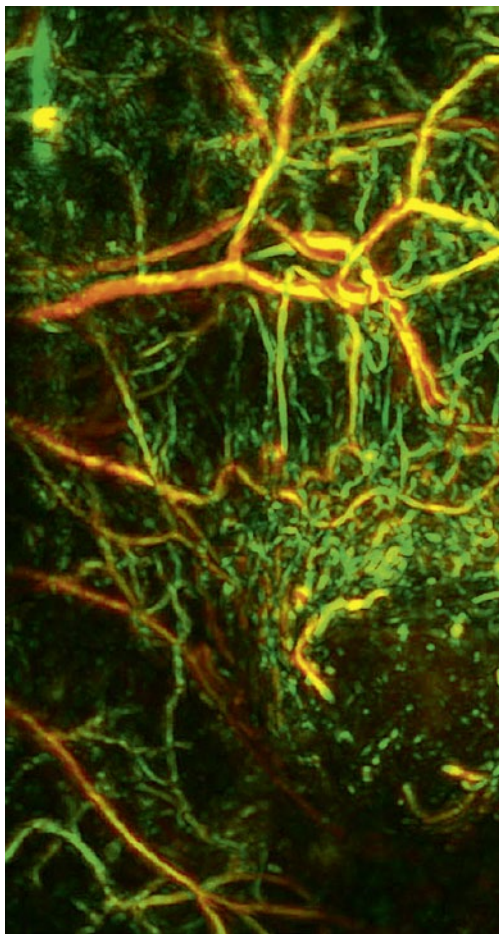
To display the images, another expert in medical imaging, Professor Dr Daniel Razansky of Helmholtz Zentrum Munich, is developing an affordable diagnostic device for clinical use in the operating room (OR). While the device today costs around €200,000, Ntziachristos considers a future price tag of €50 to be realistic. Thus, in 2011 he and two partners founded the spin-off iThera Medical in Munich to fine-tune the product for a market launch. This requires capital.

## Awards for visionary research

When it comes to raising capital, the many awards Ntziachristos, a qualified electrical engineer, has collected over the past few years obviously help to give investors peace of mind. In 2013, he received the Leibniz Prize of the German Research Foundation (DFG) and last year he was awarded – for the second time – the ERC Advanced Grant of the European Research Council.

That grant of €2.49 million will be disbursed over a period of five years. The funds will be used to develop a portable device for human patients. As to market maturity the Helmholtz Zentrum did not provide any information since the product is still under development.

While working on the marketability of the device, Ntziachristos' research is also addressing the major limitations of optoacoustics: the laser cannot penetrate deeper



*Software reads/calibrates CT or MRI scans to present a positioning plan*

# Needle placement takes six minutes

**Correct placement of needles is time consuming. So much so that researchers at the Fraunhofer Institute for Manufacturing Engineering and Automation (IPA), along with experts at Kuka AG developed a robotic assistance system that enables needle placement in only six minutes. The doctor can fully concentrate on needle insertion, with calibration and positioning carried out by a computerised system with a robotic arm.**

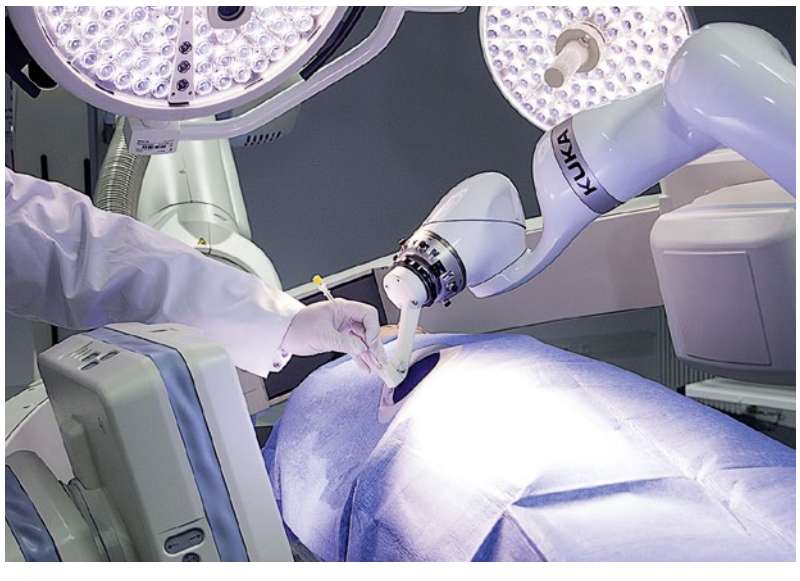
Report: Lena Petzold

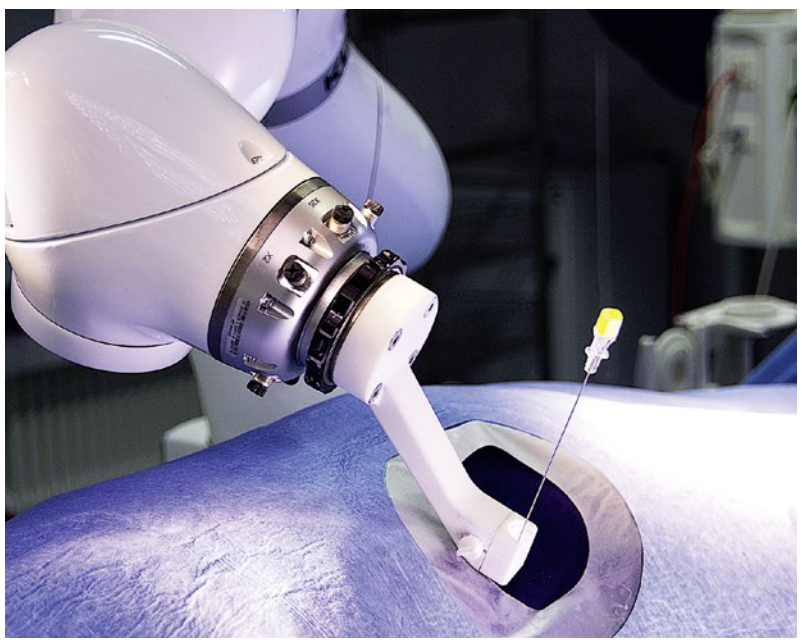
**'Correct needle positioning** for surgical interventions or biopsies is time-consuming,' explains Engineer Andreas Rothfuss, a member of the working group for Information Systems for Medical and Bio Sciences at Fraunhofer IPA. 'The angle and position must be accurate as mistakes can lead to the removal of the wrong tissue or even organ damage. The procedure can easily take half an hour. This represents a considerable chunk of time for doctors under constant time pressure, particularly as it is rarely possible to carry out these types of biopsies in a cost-effective way.' The project group for automation in medicine and biotechnology PAMB at the Institute has therefore set itself the task of simplifying these processes with digital technology.

## Finding the largest common denominator

'The difficult part of the project was the compilation of the user profile. Finding a common language for doctors and engineers, and jointly exploring the opportunities and limits of such a system, was a complicated undertaking – which we mastered step by step,' Rothfuss says. Medics and engineers continued to keep in close contact after the development of the profile.

**Focusing on needle insertion along with robotic assistance**



**When the robot holds the needle, X-rays can be obtained without the doctor's hand in the images**

'Obtaining regular input and resolving any issues arising without complications was extraordinarily helpful,' he adds, describing the Mannheim University Hospital cooperation.

## Software generates a positioning plan

The result is a system that combines the advantages of digital support with medical 'craftsmanship'. A software programme reads the patient's CT or MRI images, calibrates them and generates a positioning plan. The doctor checks the plan and releases it if there are no objections.

Images and positioning can obviously be precisely controlled in the system.

Once given the go-ahead, the robotic arm can automatically move into the correct position but can be stopped manually at any time during the process. The arm reacts to touch so that safe handling of the equipment is always guaranteed.

Once the arm is in position the doctor can push the needle into the mounting bracket and guide it into the patient's body at a precise angle. This provides human control over the process and over the tissue penetration. After the procedure the robotic arm retracts into the starting position.

## Reducing radiation exposure

The system is to cover all standard therapeutic procedures, such as ablation of metastases and other percutaneous techniques. The software can simulate not only the needle position but also the spread of heat in the tissue.

A further advantage can be seen in the control of the placement. As the robot holds the needle in position it is possible to take X-ray images without the doctor's hand obscuring the image, which reduces radiation exposure for the doctor.

The robot-guided positioning also ensures that the needle cannot slip, which means not as many X-ray images are required for control, and radiation exposure for the patient is also lower.

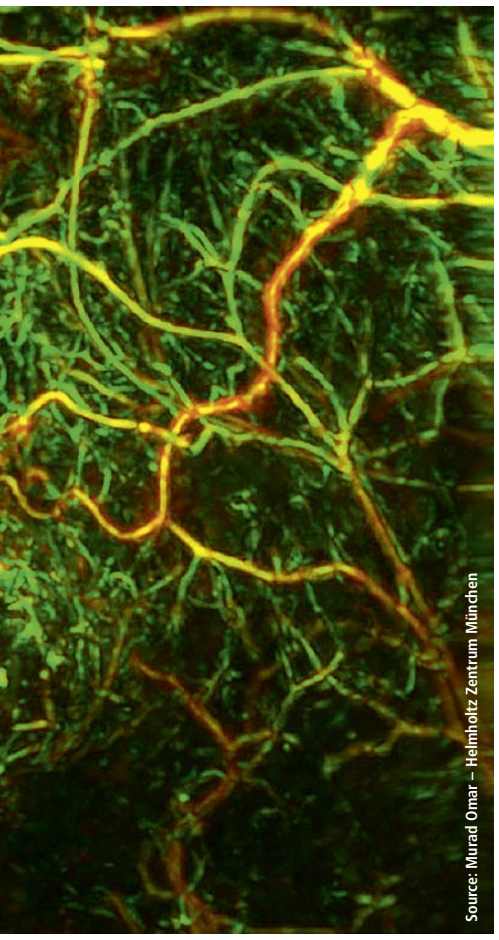
## Progress with this technique will be fast

The intuitive software and positioning groundwork not only save time but also offer valuable support to less experienced doctors.

Rothfuss is convinced that progress will be fast: 'First clinical tests are due to be carried out from spring 2018, and we hope to be ready to launch the system in three years' time.

The system has great potential – it may in time even facilitate fully automated placement.'

At the Fraunhofer Institute for Manufacturing Engineering and Automation (IPA) in Stuttgart, Germany, **Andreas Rothfuss** worked as an assistant while studying for his degree, specialising in manufacturing engineering at Stuttgart University. After joining the Project Group for Automation in Medicine and Bioengineering (PAMB) in Mannheim, Germany, in 2012, he began writing his diploma thesis, 'The evaluation of shape-memory actors with respect to possible applications in minimally invasive surgery'. He is now a doctoral researcher for the PAMB.


Source: Murad Omar – Helmholtz Zentrum München

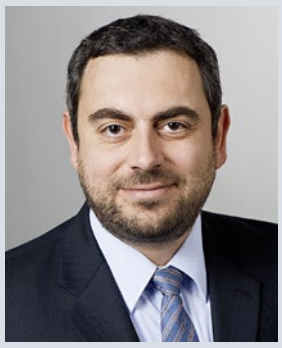
**Multi-spectral optoacoustic tomography (MSOT) could help to detect cancer cells early**

Thus, liver studies, for example, are impossible.

Ntziachristos's colleague Razansky is particularly interested in the molecular level, the biochemical reaction in the cell. Whatever the individual research interests of the two scientists are, the overarching aim of the team is early detection of diseases and tracking of disease progression so as to save time-to-diagnosis and money and above all to help patients by improving prognosis.

Additionally, the optoacoustic imaging pioneers think even further. They envisage new interdisciplinary fields of medical science and new areas of application, such as the diagnosis of inflammation or metabolic disorders and neurology.

To test their ideas the researchers successfully applied for Horizon 2020, the major European Union research and innovation programme for 2014 to 2020.



Research carried out by **Professor Vasilis Ntziachristos** encompasses the development of new methods and devices for biological and medical imaging, focusing on innovative non-invasive approaches that visualise previously unseen physiological and molecular processes in tissues. His research also aims to translate these methods to advance biological discovery, accelerate drug development and offer efficient methods for diagnostics and theranostics. Ntziachristos studied electrical engineering at Aristotle University, Thessaloniki, Greece, and gained Master's and doctoral degrees from the Bioengineering Department at the University of Pennsylvania, USA. He was assistant professor and director of the Laboratory for Bio-Optics and Molecular Imaging at Harvard University and Massachusetts General Hospital. He now directs the Biological and Medical Imaging Institute at Helmholtz Zentrum Munich, Germany.

than four to five centimetres and the sound loses quality the deeper it moves into the tissue.

# ETIM 2018

**After this year's successful first congress about Emerging Technologies in Medicine (ETIM) in Essen, Germany, the organizing committee sets the stage for the second edition on February, 16 and 17, 2018.**

**The congress will** again take place at the Lehr- und Lernzentrum of the medical faculty of University Hospital of Essen, Germany. The first day is dedicated to Artificial Intelligence and the second to Robotics. Key topics will include the role of artificial intelligence in diagnostics and the future of robot-assisted surgery.

Advances in healthcare and medical research are already strongly driven by information technology and engineering, the ETIM committee points out. Technologies like individual genome sequencing or high-performance multiparametric imaging generate exponentially growing datasets while contemporary data-mining techniques allow to extract valuable data from existing archives. These offer the opportunity for highly specific clinical decision making and personalized precision medicine. Further acceleration of medical innovation can be safely predicted. However, as complex challenges often require complex solutions, these technologies demand an interdisciplinary approach between clinicians, computer scientists, engineers, researchers, healthcare providers, legislators and many other disciplines. The 2018 ETIM will therefore provide an opportunity for experts to get together.

Detailed information is available at https://etim.uk-essen.de/.

*Medicine will be fundamentally reclassified*

# Pre-empting disease before it strikes

**Report: Cynthia E. Keen**

**Many challenges** and opportunities exist for innovation in diagnostic imaging in the 21st century. One lies in biomedicine, especially in terms of personalised medicine. Just as radiology today is essential for the diagnosis and treatment of disease, imaging's contribution to biomedicine has the potential to dramatically alter medical treatment by focusing on proactive intervention prior to disease progression, Elias A Zerhouni MD, told attendees at the opening session of the 2017 RSNA annual meeting.

Historically, innovations in diagnostic imaging have been interdisciplinary, achieved through collaborations in medical physics, chemistry, and medicine. The biomedical information clinicians need to understand the body is multidimensional. Defining bio-imaging science as 'the extraction of spatially and temporally resolved, structural and functional multidimensional biological information from molecules to humans,' Zerhouni rhetorically asked: 'How do we get biomedical imaging information at the molecular level and transfer this into an organ?'

Source: watchara / Shutterstock

He explained that the multidimensional complexity of medicine can be perceived as layers of interactivity that incorporate the DNA/RNA/ and proteins interacting with each other within a cell, and the cells interacting with tissues, organs, and the environment. There are seven or eight layers in total that need to be understood with respect to interacting with each other in varying environments. This complexity is multiplied by the number of permutations in genes and RNA. More than 50 years of research have been spent trying to understand these interactions.

'The challenge facing medicine is how to combine the need to understand the complexity while achieving precision at an individual level. This is the centre core of biomedical innovation in the 21st century. Medicine should no longer wait for disease to strike a patient, but rather pre-empt disease before it strikes.'

Zerhouni explained that it is necessary to understand individual variations in disease risks and pathways. Radiology researchers have begun to identify correlations between imaging data and genotype data.

Science is shifting from the 'hardware' to the 'software' of life. Zerhouni believes that imaging sciences will play a major role in precise reclassification of what medicine is all about: a network of molecules interacting. These are affected by genetic, infectious or autoimmune diseases and, because of their interaction complexity, diseases are not homogeneous. No one disease can be controlled by just one target, which is why the response by patients to treatments differs. Radiologists can contribute to personalised medicine by identifying the 'tools' to address targets. 'If imaging can show the interaction of every therapeutic agent and every one of their targets, and the consequences of their interaction, this 'gold mine' of information would make progress very fast. Diagnostics and therapeutics are two faces of the same coin,' he pointed out.

'Understanding molecular networks, disease pathways, and their regulation in health and disease will lead to a functional and more precise reclassification of most diseases based on their specific molecular pathways, enable predictive biomarkers discovery, and offer a greater understanding of environmental drivers,' Zerhouni said. Identification of reliable biomarkers needs to be a strategic goal of imaging innovation. A goal today of research in therapeutics is to develop 'dream molecules' that will do multiple things at once. The challenge to radiology is to localise and assess functionality of therapeutic molecules and their targets in vivo.

Multi-modality imaging biomarkers (PET/CT, PET/MRI) need to be identified and correlated with biological markers. Zerhouni predicted that diagnostic imaging departments in academic research organisations would have their staff dedicated to this.

With respect to machine-augmented diagnostics and artificial intelligence (AI), Zerhouni predicts that in 5-10 years its use will become standard in radiology. He sees the technology as being able to improve radiologists' performance and to help standardise levels of performance.

He predicts that huge global reference databases queried by AI will enable radiologists within seconds to compare an exam they are interpreting with a wealth of stored and relevant-to-patient data. 'I see a future where a radiologist will say in a radiology report that the patient corresponds to RSNA Reference Database Number xxxxx. Radiologists will be able to track the evolution of disease and extract novel information.'

Zerhouni concluded by offering this advice to the RSNA meeting attendees:

- Ask not what radiology can do but what this discipline should do

*Radiographers gain a European diploma by 2019*

# Levelling EU qualifications

**Radiographers are increasingly central to patient care, but the heterogeneous education and skills across Europe remain challenging. Dr Jonathan McNulty and Håkon Hjemly, of the European Federation of Radiographers Societies (EFRS), explained how they plan to improve radiographers' visibility and work towards homogenising training across Europe, notably by launching a European Diploma in Radiography by early 2019.**

**Report: Mélisande Rouger**

**Radiographers are key** team players in medical imaging, nuclear medicine and radiation therapy, and their role is growing, boosted by the rising demand for imaging studies and procedures and the continuous shortage of radiologists in many countries. But radiographers have many faces and names, and this compromises the recognition of their skills across healthcare, according to Jonathan McNulty, EFRS newly elected president.

'The official title we use is radiographer, but there are 20 or more other titles for the profession! Radiographers can also be nurses, technicians, radio manipulators (…) and may provide very distinct services depending on the country.'

Not only does the profession have multiple identities, but also education varies considerably across Europe. While some countries offer masters or doctoral qualifications specifically for radiographers, other countries only have two-year programs for entry into the profession and sometimes do not even provide a national board registration.

'We have a very complicated jigsaw here,' McNulty summed up.

The EFRS plans to change this by promoting a bachelor's level as the entry level to the profession, versus shorter, vocational qualifications; meaning it will require a minimum three-year program at level 6 in its European qualification framework (EQF) benchmarking document. The organisation has also introduced an EQF level 7 (masters level) benchmarking document, in a move to raise the bar for future generations.

'We very strongly feel that radiographers across Europe should be trained to the highest possible level. That allows them to make a greater contribution to healthcare and to enhance radiology and radiation therapy services. The profession must be duly regulated,' McNulty said. 'A bachelor's level qualification is seen as the minimum standard for us; it should be the entry level to the profession, but it's still not the case in some countries.'

To make up for the gap between seasoned radiographers, who had their qualification decades ago, and what they want the profession to look like from now on, the EFRS is also working on the practicalities of launching a European Diploma in Radiography very soon, which was among topics discussed by the federation during its last annual business meeting, in November in Alcalá de Henares near Madrid. 'This remains one of our major objectives. We hope to progress this through 2018, with a view to launching in 2019. Radiology has such a diploma, medical physics has it too, so it's something we want to certify as a certain standard of professional radiography knowledge in Europe,' McNulty explained.

**The lack of homogeneity in European radiographers' education has become a pressing issue, as the unequal distribution of professionals leads to migration**

Taking the diploma could be useful for those who only received a two-year education in their countries but have 20-year experience. 'The diploma could help show that they have what the EFRS sees as minimum level of knowledge for the practice of radiography,' he added.

Continued professional development (CPD) is also instrumental in securing high professional standards across Europe and it should be homogenised too, according to Håkon Hjemly, immediate past president of the EFRS. 'It's necessary to maintain and renew your skills and CPD is an excellent system for that. This is something that many countries have mandatory, but many still don't,' he said.

The lack of homogeneity in European radiographers' education has become a pressing issue, as the unequal distribution of professionals leads to migration, which can prove tough when countries have different curricula.

'About 50% of our member societies have a shortage of radiographers and the other half is producing too many. In Italy, for instance, many radiographers who qualify struggle to find work and many will have to work for free to get a foot through the door. Consequently, many have come to Ireland and the United Kingdom for a job but, for others, their qualification may not be recognised because it may not be equivalent to bachelor level,' McNulty explained.

Having the same education could also help improve the profession's profile among medical specialties. Radiographers are simply underutilised, yet research shows they would have the skills to take on more responsibilities, according to McNulty. 'I feel quite strongly how under-utilised and under-valued radiographers are. There is not enough recognition of our knowledge and skills in some countries, whereas in others radiographers are involved in reporting

With a master's in clinical health and postgraduate education in digital imaging processing and X-ray protection **Håkon Hjemly** is Manager of Policy for the Norwegian Society of Radiographers, covering health political issues and radiographers' role development. Earlier, he worked in Norway's private and public sector, as clinical radiographer, QA-administrator, manager, radiation protection officer, product specialist and sales rep. (CT, Mammography, C-arm), and pioneered identifying pitfalls and quality assurance controls for medical imaging digitisation at X-ray departments. He has chaired and delivered numerous presentations at international conferences. Håkon was elected member of the EFRS election committee in 2010, then Treasurer in the 2011-2014, and then EFRS Vice-President in 2014-2015 and President in 2015-2017.

**Elias A Zerhouni MD** is a world renowned leader in radiology and medical research, who has helped change perceptions of the importance of imaging science within the global medical community, He is president of Global Research and Development at Sanofi, the Paris-based global pharmaceutical company in France. He has developed innovations in both computed tomography (CT) and magnetic resonance imaging (MRI) to improve diagnosis of cancer and cardiovascular disease. As director of the USA's National Institutes of Health (NIH) from 2002 to 2008, Zerhouni launched the NIH Roadmap for Medical Research, an initiative designed to transform the translation of research into medical practice.

in the 21st century.

- Remain the key integrator that can improve healthcare for patients through imaging.
- Participate in solving core scientific challenges of today.
- Train and proactively mentor the next generation of radiologists, because they will represent the future of radiology in the 21st century.

**Dr Jonathan McNulty** is Associate Dean for Graduate Taught Studies and Head of Subject, Radiography in the School of Medicine, University College Dublin, Ireland. He oversees more than 75 postgraduate programs and continuing professional development activities across the school. He is President of the European Federation of Radiographer Societies (EFRS), and Board Member since 2014. He chaired the Education Wing, a network of 59 educational institutions within the EFRS, and Vice-President from 2016-2017.

imaging examinations and performing certain procedures traditionally done by medical doctors.

'The impact radiographers can have on hospitals is dramatic. A lot of research shows that, when radiographers take on advanced practices such as these, it can result in efficiencies, save time and money, and well trained radiographers have been shown to perform such tasks as well as radiologists. Ultimately radiographers may improve patient care by providing a more timely report in certain instances,' he said.

Recognising radiographers' skills could be pertinent in countries with an acute shortage of radiologists, based on the experience of cooperation between radiographers and radiologists in the UK or Ireland, for example. In the end, a collaborative approach can only benefit healthcare, McNulty concludes.

*In 335 high-risk lesions the system correctly diagnosed 97% as malignant*

# Artificial Intelligence helps to detect breast cancer

**Scientists are using Artificial Intelligence to support more effective breast cancer detection. The researchers at Massachusetts Institute of Technology (MIT) Computer Science and Artificial Intelligence Laboratory (CSAIL), Massachusetts General Hospital (MGH), and Harvard Medical School, are using the machine learning system to predict whether breast lesions identified from a biopsy will turn out to be cancerous, Mark Nicholls reports**

**The hope now** is that this research could help reduce the number of unnecessary breast cancer surgeries because it could pinpoint which lesions are cancerous more accurately and more efficiently.

In the study, the system was trained on information about such lesions and looked for patterns among a range of data points, including demographics, family history, biopsies and pathology reports.

When tested on 335 high-risk lesions, it correctly diagnosed 97% as malignant.

The researchers suggest that such levels of accuracy could lead to a reduction in the number of unnecessary surgeries by more than 30%.

While mammograms can detect cancers, there is also a risk of false positive results that can lead to unnecessary biopsies and surgeries – often from 'high-risk' lesions that appear suspicious on mammograms and have abnormal cells when tested by needle biopsy. The researchers say patients have the lesion surgically removed but often it is benign and the operations were unnecessary.

To address this, the team developed the machine learning system to predict if a high-risk lesion identified on needle biopsy after a mammogram will upgrade to cancer at surgery.

'Because diagnostic tools are so inexact, there is an understandable tendency for doctors to over-screen for breast cancer,' Dr Regina Barzilay, MIT's Delta Electronics Professor of Electrical Engineering and Computer Science, pointed out. 'When there's this much uncertainty in data, machine learning is exactly the tool that we need to improve detection and prevent over-treatment.

'A model like this will work anytime you have lots of different factors that correlate with a specific outcome. It hopefully will enable us to start to go beyond a one-size-fits-all approach to medical diagnosis.'

Using a method known as a 'random-forest classifier', the model resulted in fewer unnecessary surgeries compared to the strategy of always doing surgery, while also being able to diagnose more cancerous lesions than the strategy of only doing surgery on traditional 'high-risk lesions'.

Dr Constance Lehman, Professor at Harvard Medical School and chief of the Breast Imaging Division at MGH's Department of Radiology added: 'To our knowledge, this is the first study to apply machine learning to the task of distinguishing high-risk lesions that need surgery from those that don't. We believe this could support women to make more informed decisions about their treatment, and that we could provide more targeted approaches to healthcare in general.'

It is hoped that MGH radiologists will begin incorporating the model into their clinical practice over the next year. 'In the past, we might have recommended that all high-risk lesions be surgically excised, Lehman said. 'But now, if the model determines that the lesion has a very low chance of being cancerous in a specific patient, we can have a more informed discussion with our patient about her options. It may be reasonable for some patients to have their lesions followed with imaging rather than surgically excised.'

The team – which also included Manisha Bahl, director of the Massachusetts General Hospital Breast Imaging Fellowship Program - says that they are working to further evolve the model and in future hope to incorporate the actual images from the mammograms and images of the pathology slides, as well as more extensive patient information from medical records.

(Photograph: Jason Dorfman/CSAIL)

From left:

**Manisha Bahl** MD is a breast imaging radiologist and director of the Breast Imaging Fellowship Program at Massachusetts General Hospital/Harvard Medical School in Boston, USA. After graduating from the Harvard School of Public Health with an MPH in Health Policy and Management, she completed a radiology residency and breast imaging fellowship at Duke University Medical Centre and joined the faculty at Massachusetts General Hospital/Harvard Medical School in July 2016.

**Regina Barzilay MD** is a Delta Electronics Professor in the Department of Electrical Engineering and Computer Science and a member of the Computer Science and Artificial Intelligence Laboratory at the Massachusetts Institute of Technology. USA. Her research focuses on natural language processing, applications of deep learning to chemistry and oncology.

**Constance Lehman MD** is a Professor at Harvard Medical School in Boston, USA, and chief of the Breast Imaging Division at MGH's Department of Radiology. After graduating from Duke University and receiving medical and doctoral degrees at Yale University, she became Professor and vice chair of Radiology and division chief of Breast Imaging at the Seattle Cancer Care Alliance before her recent move to Massachusetts General Hospital.

*Defining which breast cancer patients could gain from immunotherapy*

# The DNA mismatch repair mechanism

**Report: Mark Nicholls**

**A new genetic study** by UK-based scientists suggests that immunotherapy drugs could prove to be an effective treatment for some breast cancer patients.

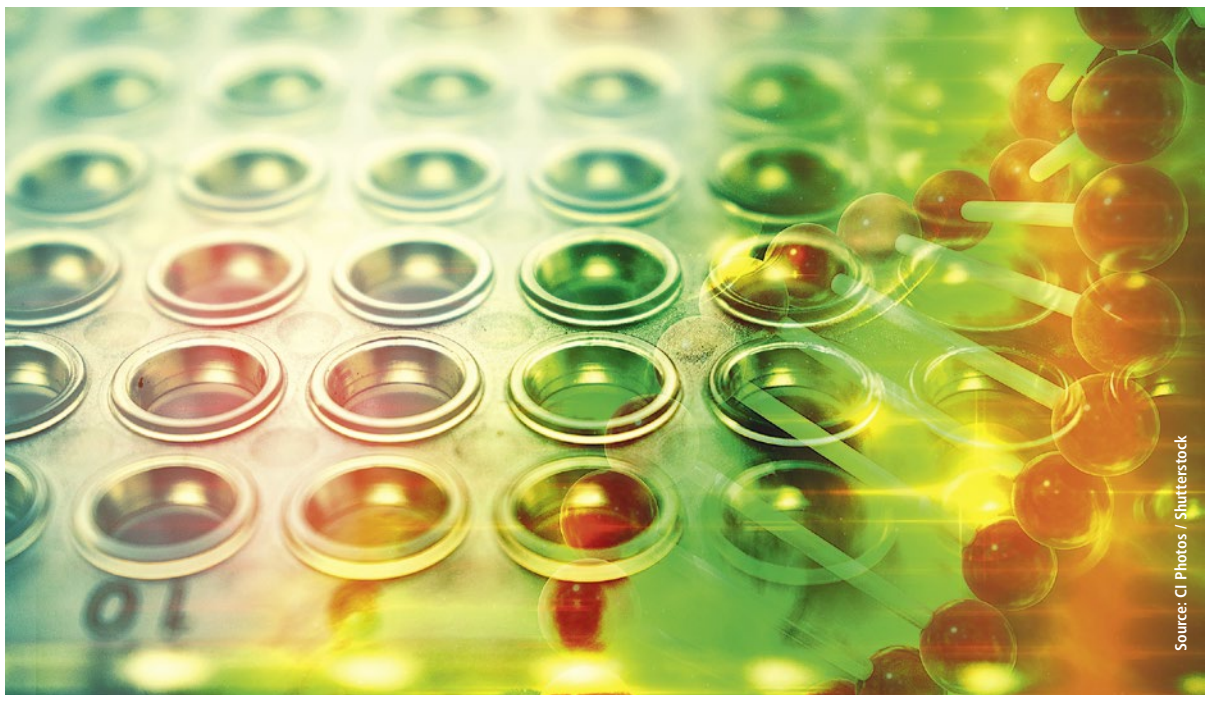
Scientists from the Wellcome Trust Sanger Institute, near Cambridge – one of the world's leading genome centres – and their collaborators, have identified particular genetic changes in a DNA repair mechanism in breast cancer.

Led by Dr Serena Nik-Zainal, the researchers suggest it could open up the possibility of another therapy option for around 1,000 UK breast cancer patients who could benefit from existing drugs.

The study found that a particular group of breast cancer patients have genetic changes, or mutations, that occur due to an abnormality of a DNA repair mechanism known as mismatch repair, which is a mechanism to recognise and remedy mistakes in the genetic code that arise during DNA replication and recombination. The mechanism also repairs some forms of DNA damage.

When cells lack the mismatch repair pathway, mutations build up, which results in cancerous tumours formation. These mutations are found in other cancers, such as colorectal cancer, but are rarely looked for in breast cancer.

In recent work in the USA, colorectal cancers with deficient mismatch repair have been treated with immunotherapies, which exploit the fact that, under the influence of these so-called check point inhibitors, highly mutated tumour cells can be recognised as 'foreign' by the patient's immune system. The results of this new Sanger Institute study suggest that these immunotherapies could also be effective for some breast cancer patients, based on the same mutation patterns seen in their tumours.



Source: CI Photos / Shutterstock

**The researchers analysed the whole genome sequences of 640 breast cancer tumours and looked for patterns in the mutations**

'We've unequivocally found mismatch repair deficient breast cancers,' Serena Nik-Zainal said 'As these tumours have the same mutational signatures as those of other cancers, like colorectal cancer, in theory they should respond to the same immunotherapy drugs.

'Our results suggest expanding the cohort of cancer patients that could possibly be treated with checkpoint inhibitors to include these mismatch repair deficient breast cancer patients.'

The study researchers analysed the whole genome sequences of 640 breast cancer tumours and looked for patterns in the mutations, known as mutational signatures, which indicated abnormalities in the mismatch repair mechanism.

From the mutational signatures, the team identified 11 tumours that had the mismatch repair defects causing the breast cancer.

'Using whole genome sequencing we can start to stratify breast cancer patients into different categories based on their mutational signatures,' said one of the researchers Dr Helen Davies, from the Wellcome Trust Sanger Institute. Current clinical criteria means these tumours would not have been detected as being deficient in the mismatch repair pathway. We have shown that there is, in fact, another category of breast cancers – those with defective mismatch repair.'

Professor Karen Vousden, chief scientist at Cancer Research UK (CRUK), added: 'Immunotherapies have shown promise for some cancer patients, but the challenge for doctors has been predicting which patients they are likely to help. This study reveals more about the genetic patterns that could show which women with breast cancer are more likely to respond to immunotherapy treatments.'

The next step is to stage clinical trials to determine if immunotherapies could help selected breast cancer patients.

The Wellcome, CRUK, Dana-Farber/Harvard Cancer Centre SPORE in Breast Cancer, and National Research Foundation of Korea with grants from the Korean government, supported this research project.

**Serena Nik-Zainal MD** is a Career Development Fellow (CDF) Group Leader in the Cancer Genome Project at the Sanger Institute in Cambridge and an Honorary Consultant in Clinical Genetics at nearby Addenbrookes Hospital, UK. Having qualified in medicine from the University of Cambridge in 2000, trained as a physician and subsequently specialised in Clinical Genetics, she undertook a PhD at the Wellcome Trust Sanger Institute in 2009. Her research focuses on pursuing biological understanding of the mutational signatures that have been identified in primary human cancers, with a specific interest in breast cancer.

*Mastectomies due to 'family history' could drop by a third*

# DNA test is 'a massive game changer'

**Report: Mark Nicholls**

**A new genetic test** to assess breast cancer risk in women who have a family history of the disease could be introduced into clinical practice in the UK within the next few months.

Devised at Manchester University NHS Foundation Trust (MFT) and the University of Manchester, researchers believe the test for high-risk groups could also help reduce the number of women needing to have surgery to remove their breasts. By narrowing down their risk, women will be better informed about whether to have a mastectomy, or not, explained Professor Gareth Evans, who led the work that resulted in the new test.

Scientists say the test will accurately predict breast cancer risk in women who do not test positive for BRCA1/2 gene mutations and, in some cases, may also help to refine breast cancer risk in those with the BRCA1/2 mutations.

The most common cancer that affects women having a parent or sibling with breast cancer makes women twice as likely to develop breast cancer themselves. Mutations in the BRCA1/2 genes have been identified as a cause of hereditary cancer, but only account for 15-20% of the underlying inherited genetic trigger for the condition.

**The test is supposed to help women at risk of familial breast cancer to make more informed decisions about their care**

The new genetic test assesses breast cancer risk based on genetic variations - single nucleotide polymorphisms (SNPs) - in an individual's DNA.

Researchers found that mutations of 18 SNPs were indicative of breast cancer risk for women who did not carry BRCA1/2 mutations. These were found to have minimal effect in isolation, but when combined could increase or decrease breast cancer risk considerably.

The study recruited 451 women (112 with BRCA1/2 mutations) with a family history of breast cancer who had developed breast cancer. The researchers compared the diagnosis of invasive breast cancer and genetic profile in the case group against that of a control group of 1,605 women (691 with BRCA1/2 mutations).

The analysis of DNA using participants' blood samples was used to determine their individual genetic makeup and predict an overall risk estimate alongside other risk factors such as age at first assessment, family history of first and second-degree relatives, age at first child, first period and menopause, height and weight, and history of prior non-cancerous breast disease.

From the findings, women originally viewed as at high risk (lifetime risk of 30% or greater) were reclassified to a lower risk, where mastectomy is not recommended to reduce the risk.

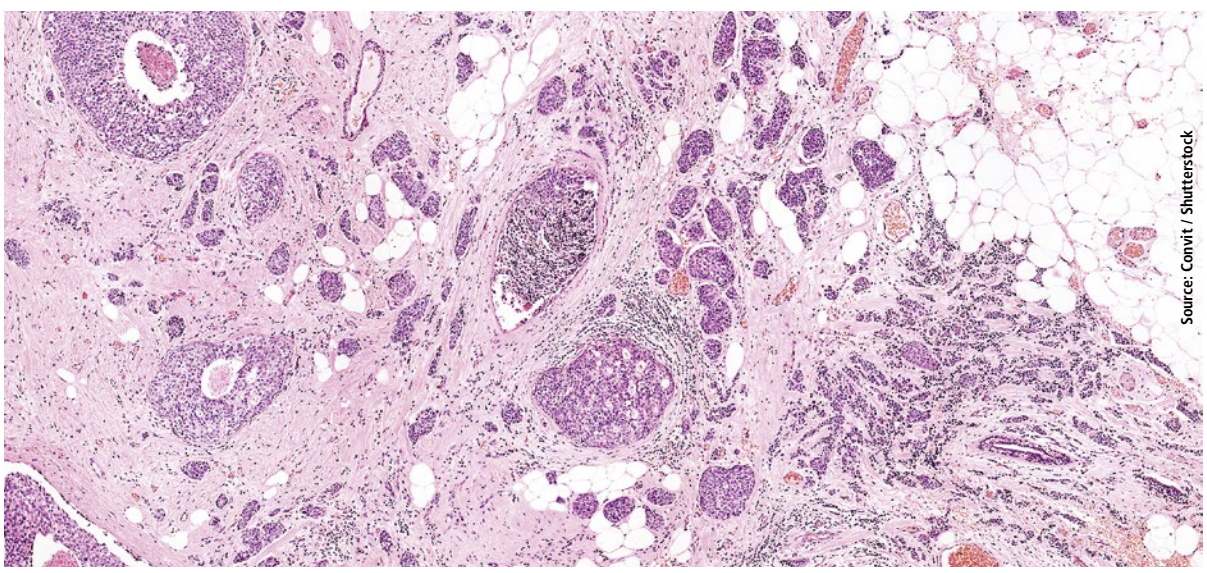
The study suggested that the number of women with BRCA1/2 mutations who currently choose to have a mastectomy could now fall by a third from 50% to 36%.

Professor Evans, a Consultant in Medical Genetics and Cancer Epidemiology at The University of Manchester and the city's Saint Mary's Hospital – where the test will first be made available – said: 'This new test will help women at risk of familial breast cancer to make more informed decisions about their care.

'BRCA1 and BRCA2 are just part of what we should be looking for when assessing risk and in Manchester we plan to incorporate screening for these new genetic markers in clinical practice within the next six months.

'We are committed to improving cancer prevention through research and, with funding from the NIHR Manchester Biomedical Research Centre, we plan to develop new screening strategies and biomarkers for other common cancers, including womb, bowel, ovarian and prostate.'

Professor Evans is hoping the test will become more widely available, and describes it as a 'massive game changer for breast cancer', which can accurately assess risk in the whole population from those with a family history and those with BRCA mutations.



Source: Convit / Shutterstock

**Gareth Evans** is Professor of Medical Genetics and Cancer Epidemiology at the University of Manchester, UK, and Consultant in Medical Genetics and Cancer Epidemiology, Central Manchester Hospitals NHS Foundation Trust and The Christie NHS Foundation Trust. He has an international reputation in clinical and research aspects of cancer genetics, particularly in neurofibromatosis and breast cancer, in which his group is particularly interested in biomarkers that indicate the risk of developing breast cancer.

*Acceptance recognised in new recommendations*

# MRI's role in prostate cancer diagnosis

**LLars Schimmöller MD, associate professor of radiology at Düsseldorf University Hospital, tackled current diagnosis of prostate cancer (PCa) and addressed tumour detection, staging, active surveillance and recurrence during the Medica Academy session on Imaging Update. He also highlighted how MRI helps improve biopsies and avoid unnecessary surgery in PCa.**

Interview: Mélisande Rouger

**Asked about the** latest advances in PCa diagnosis, Professor Lars Schimmöller spoke of 'a remarkable change' – the increasing role of magnetic resonance imaging (MRI) in routine clinical diagnosis. 'In its updated guidelines, which will be published later this year, the German Society of Radiology notably insists on the importance of multiparametric MRI (mp-MRI) and MRI-guided biopsy for PCa diagnosis.

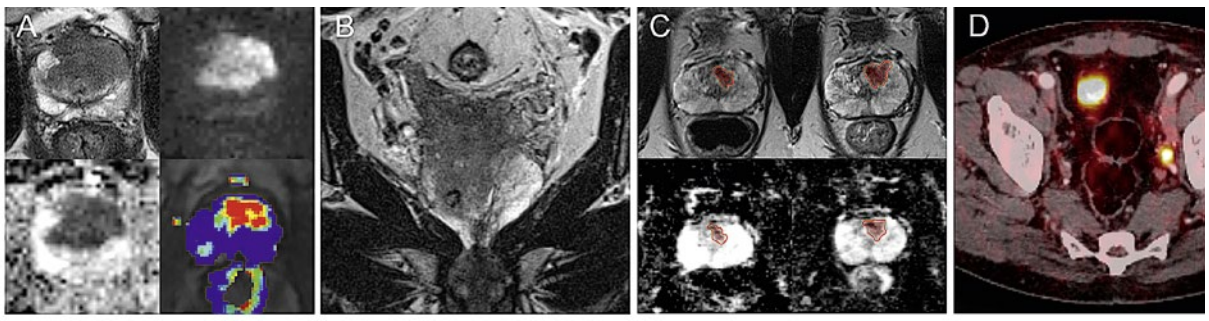
'The new recommended technical approach is that mp-MRI can not only be used but also should be used in secondary PCa detection after negative transrectal ultrasound (TRUS)-guided biopsy and before inclusion of patients for active surveillance, similar to international guidelines. Moreover, the German preliminary recommendations for 2017 state that mp-MRI can be used for primary PCa detection as long as quality standards are fulfilled. Based on these requirements, urologists can and should perform targeted biopsies of MRI suspicious lesions, by using either the cognitive approach (fusion of MRI and US in mind) with TRUS or software-based MRI-US fusion-guided biopsy approach.

'Five to ten years ago, the standard was to just measure prostate-specific antigen (PSA) value, carry out digital rectal examination, and then an ultrasound and US-guided systematic biopsy. The problem with systematic biopsy is that especially the anterior and apical parts of the prostate are not covered, and cancers missed or only partially captured with up to 50% false positive lower grade histology, so that you never know if higher-grade proportions of the tumour exist.

'One of the big challenges in PCa is its biology. When you have multifocal tumour cells, which are quite common, it's hard to get the real imaging of where the index lesion is located. Performing an MRI-guided biopsy and an mp-MRI examination before biopsy to help prepare it enables it to hit a tumour with more precision. If you have quality mp-MRI, you can say with over 95% accuracy if there is clinical relevant cancer or not.

'Also, if you carry out an MRI examination before you do a biopsy, you may discover the reason for high PSA value. Sometimes it may just be prostate enlargement or an infection. So carrying out an MRI scan may also avoid performing unnecessary biopsies.

'Another significant advance in PCa diagnostics has been the use of prostate specific membrane antigen (PSMA) as a relatively new tracer to check PCa recurrence.'




**A: Detection: Multiparametric MRI with T2-weighted image, ADC-map, high b-value image, and perfusion-map showing a large anterior prostate cancer in a patient with negative systematic biopsy**
**B: Staging: Extensive seminal vesicle invasion and lymph node metastases on a coronal T2-weighted turbo spin echo (TSE) MR-image**
**C: Active Surveillance: Tumour increase in size and aggressiveness (ADC-value decrease) in follow-up MRI in a patient with bioptic verified low-grad prostate cancer**
**D: Recurrence: PSMA-PET/CT with parailiac lymph node metastasis on the left side**

## Which diagnostic and imaging modalities do you use in PCa?

'The PSA determination is the basic diagnostic tool for PCa check-up, but PSA is specific to the prostate gland and not prostate cancer. An elevation of PSA does not have to be associated with PCa, but when you use it wisely, it is an easy and excellent test for a preselection.

'The role of PSA screening has been extensively discussed, especially in over diagnosis and over treatment, but trial results from large European studies have shown the relevance of this test. We are currently trying to figure out when it makes sense and in whom – in patients aged 40, 45, 50 or 55 years?

'Ultrasound is the standard urologic imaging modality, but US has limitations in PCa detection. It is not so good for sensitivity or specificity, even combined with contrast agents. Currently none of these additional US-tools are recommended for primary PCa detection. US is primarily used to guide biopsy.

'Computed tomography (CT) only makes sense in combination with PSMA-PET, e.g. for PCa recurrence, or it may be chosen for pre-operative staging. CT is easily available and gives you an idea of metastases of bone lesion or lymph node metastasis in patients with extensive disease. But lymph nodes imaging is challenging, because they are often very small. CT is mostly not good at differentiating whether they are tumours or not in the prostate setting.

'Mp-MRI is currently the best imaging tool for prostate cancer detection, especially clinical relevant PCa. Qualitative mp-MRI is extremely promising for active surveillance and furthermore it is good for local staging. It can also help in unclear cases or PCa recurrence.

'PSMA-PET is the most promising imaging tool for PCa-recurrence and may be used for detection in unclear cases with high PCa suspicion. Combination of PSMA-PET with MRI might be very nice, but PET/MRI is rarely available and its clinical benefit remains to be demonstrated.'

## Screening programs in Germany

'The updated recommendation is that men of at least 45 years of age and a life expectancy of more than 10 years should be informed on the possible benefits and drawbacks of early-detection measures of prostate cancer like PSA determination.

'We are performing a huge national prospective multicentre randomised trial on early PSA screening in young men. Currently we have over 30,000 patients enrolled. The study is called PROBASE and we try to assess if it makes sense to measure baseline PSA for risk-adapting PSA screening. Screening must help lower mortality. It only makes sense if you help people not to die or die later from that cancer. 'PCa is most often a slow growing tumour, so that's why screening studies results need so long to show their value. You need at least 10 to 15 years approximately to show if a patient benefits from screening.'

**Lars Schimmöller MD** is Associate Professor of radiology and head of the uroradiology working group at Düsseldorf University Hospital, Germany. His research fields include multiparametric magnetic resonance Imaging (MRI) of the prostate, image-guided prostate biopsy, hybrid imaging (e.g. PSMA-PET), urogenital radiology and cancer imaging.

## What are PCa imaging risks?

'Nationwide coverage of qualitative mp-MRI examinations and qualitative standardised reporting are two of the most important challenges in PCa imaging. Furthermore, the subsequent correct targeted biopsy is also a challenge for urologists and radiologists.

'A further issue is that the biology of prostate tumours is often multifocal and/or heterogeneous in histology, and sometimes hard to differentiate from inflammation or atypical stromal hyperplasia. It is also complex to determinate the possible metastatic clone with current technology. It's crucial to differentiate tumours that are life limiting from those who are not.

'Mortality in PCa is often due to late cancer detection or inaccurate diagnosis. But most tumours are not life limiting or can be treated.

'Radiation risk, as a general limitation or challenge in radiology, is not a problem, because these patients are usually not young and MRI, as the best imaging tool, does not use radiation.'

*Brain MRI-mining helps to identify and classify ADHD*

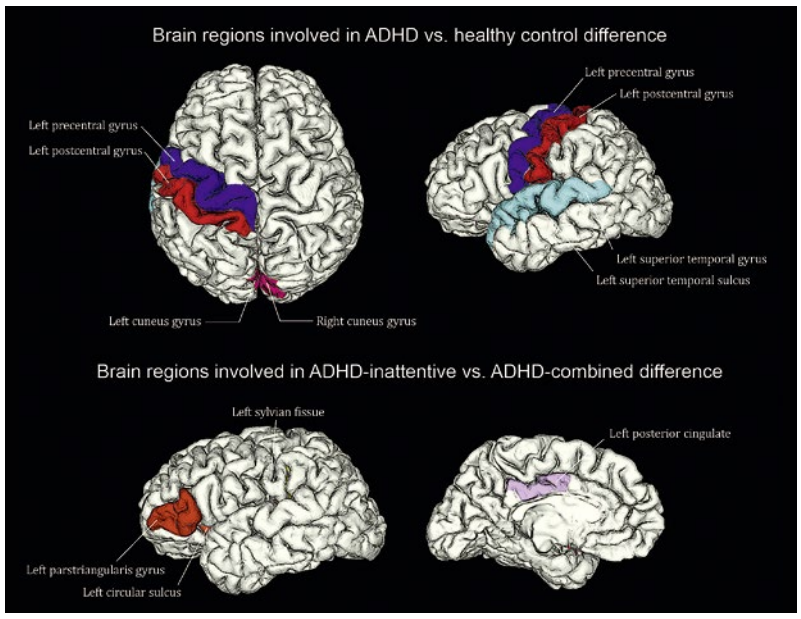
# The birth of psychoradiology

**The emerging field of psychoradiology is taking a major step ahead. A new study highlights MRI's role in identifying people with attention deficit and hyperactivity disorder (ADHD) and classifies subtypes of the condition, a leading Chinese researcher explained at the ESMRMB annual meeting. Mélisande Rouger reports**

**Advances in MRI technology** enable the detection, evaluation and follow-up of mental illnesses and psychiatric conditions. Recently, Chinese researchers have been able to identify and distinguish among subtypes of ADHD, thanks to data extracted from MRI scans.

Qiyong Gong, a radiologist at the West China Hospital, Sichuan University, revealed the details of a study he co-authored with colleagues Huaiqiang Sun and Ying Chen, ahead of its online publication in Radiology. The researchers used radiomics, i.e. the extraction of a large amount of quantitative information from digital imaging features that can be mined for disease characteristics. Gong and colleagues believe cerebral radiomics could improve diagnosis accuracy and help initiate adequate treatment earlier in patients with ADHD. 'Earlier detection means earlier prediction. Using radiomics extracted from MRI scans, we can build and evaluate classification models based on pathological subtyping. These models can then assist the psychologist in diagnosing and subtyping ADHD,' Gong explained.

The researchers examined 83 children aged 7-14 with newly diagnosed and never-treated ADHD, including children with the inattentive ADHD subtype (ADHD-1) and the combined subtype (ADHD-C). The scientists compared these MRI results with those of a control group of 87 healthy children of the same age, and screened relevant radiomics signatures from more than 3,100 quantitative features extracted from the grey and white matter.




**The brain regions related to differences are plotted on a 3-D brain model**

While they found no overall difference between ADHD and controls in total brain volume or total grey and white matter volumes, Gong, Sun and Chen observed alterations in the shape of the left temporal lobe, bilateral cuneus and areas around left central sulcus. These differences contributed significantly to distinguishing ADHD from typically developing controls.

Within the ADHD population, features involved in the default mode network and the insular cortex significantly contributed to discriminating the ADHD inattentive subtype from the combined subtype. Results highlight the accuracy of the method: researchers could discriminate patients with ADHD with control subjects with 73.7 percent accuracy and to discriminate ADHD-1 from ADHD-C patients with over 80.1 percent accuracy. 'These results are quite significant for future management and treatment of ADHD, and confirm psychoradiology will become a major tool in assisting clinicians to objectively diagnose as well as monitor the condition,' he said.

During his ESMRMB talk Gong reviewed advances in this new field of radiology, which relies on imaging data analysis rather than visual inspection of images, particularly in imaging schizophrenia.

## Schizophrenia

Ever since CT identified bilateral ventricular enlargement in patients with schizophrenia in 1976, imaging techniques have improved and the number of descriptions of structural or neuroanatomical abnormalities in mental illness has increased tremendously.

Advances in MRI, particularly functional MRI (fMRI), MR spectroscopy, perfusion mapping, diffusion-tensor imaging (DTI) and tractography, have enabled to identify functional abnormalities particularly in patients with schizophrenia.

'Studies have shown a neuroanatomical signature of schizophrenia across different ethnic groups. DTI has recently showed micro-structural differences between the brains of healthy patients and those with schizophrenia, including superior longitudinal fasciculus and inferior fronto-occipital fasciculus. However, there is dissociation between altered regions seen on structural studies and functional studies in default mode or fronto-parietal networks, and we must be aware of that,' he said.

MRI techniques have also enabled identification of cerebral abnormalities after antipsychotic treatment, notably after two-year treatment, according to Gong. 'We have observed greater loss of grey matter volume and increase in cerebrospinal fluid in the frontal lobe.

'In the brain of patients with long-term schizophrenia who have never been medicated, we have also observed accelerated age-related decline in prefrontal and temporal cortical thickness, suggesting a neuroprogressive process.'

Findings highlighting functional changes after short-term (six weeks) treatment significantly correlated with improvement of symptoms, Gong added. And, when looking for regional functional changes after one-year treatment, studies have shown that amplitude of low frequency fluctuations (ALFF) in the three brain areas at baseline was significantly and positively related to the magnitude of the changes in ALFF, according to Gong. MRI also picked functional connectivity changes after one-year treatment.

Research has also shown that structural changes remained relatively stable in the early years after a first episode of schizophrenia and became progressive in the later phase of illness. Functional changes, which may reflect physiological alterations related to clinical status, are more sensitive to reflect the effects of treatment on the brain, Gong pointed out.

In the future, imaging-based disease classification will gain importance vs. diagnostic and statistical manual of mental disorders. Standardisation will be necessary to clinically validate these techniques, but they will prove useful as they advance, in particular in data acquisition and analysis. Interventional psychoradiology will also develop, Gong predicted.

'Image-guided interventions will be the next big thing. Psychoradiology will help to deeply understand the mechanisms of schizophrenia, provide objective detection and early diagnosis and enable prognosis and early treatment.

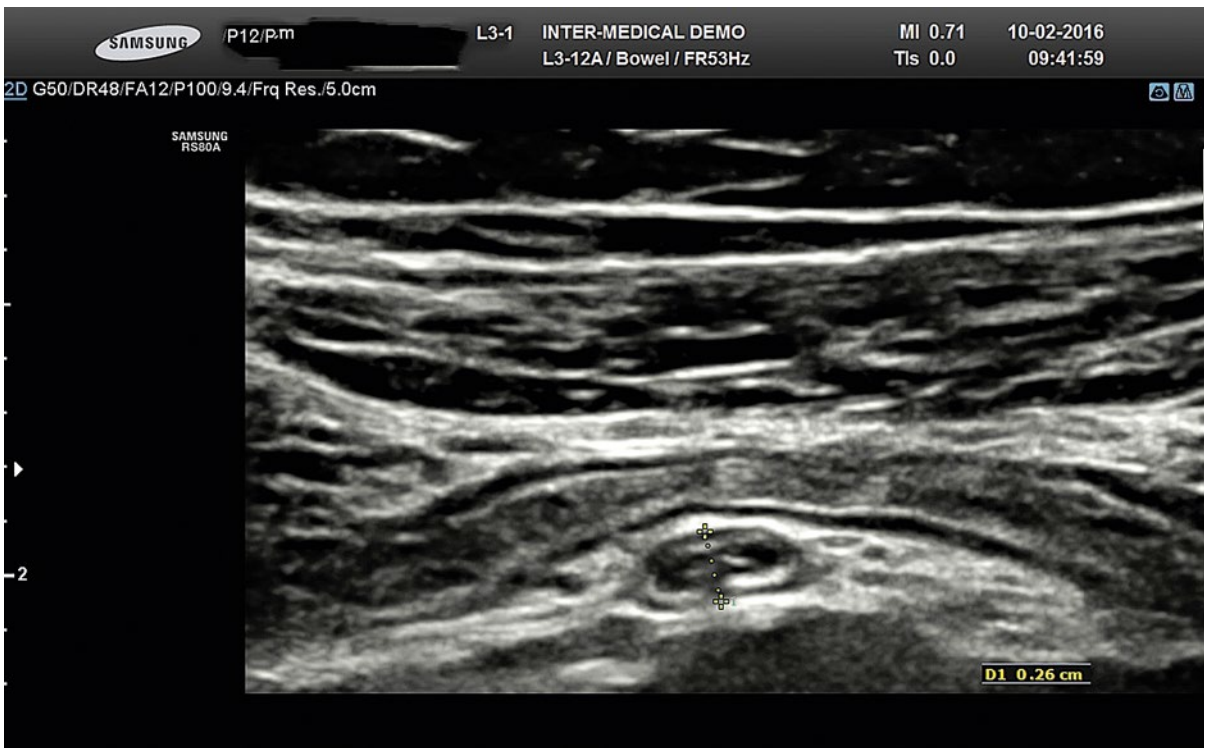
'Psychoradiology will also bring new information on other psychiatric conditions, such as depression, bipolar and borderline personality disorders, and mental health in general, for instance individual cognition, behaviour and fluid intelligence,' Gong concluded.

**Qiyong Gong MD, PhD** is Professor of radiology at the West China Hospital at Sichuan University (China). His research has focused on imaging of neuropsychiatric disorders with the innovative utilisation of MRI for mental illnesses, contributing to psychoradiology. He has published over 300 peer-reviewed articles, which, in the last five years, have received over 10,000 citations. As a member of the mainstream professional organisation, the International Society of Magnetic Resonance in Medicine (ISMRM), Professor Gong was awarded the ISMRM New Horizons Lectureship in 2015, and the Fellowship of ISMRM in 2016. He is now Secretary and Future Chair of the ISMRM Governing Committee of the Psychiatric MR Study Group.

*The first ever guidelines on gastrointestinal ultrasound*

# The EFSUMB's nineteen GIUS recommendations

**Ultrasound of the gastrointestinal (GI) tract is advancing with the development of elastography and contrast agents. Odd Helge Gilja, director and senior consultant at the National Centre for Ultrasound in Gastroenterology at Haukeland University Hospital, Bergen, Norway, has worked with the technique for the past fifteen years. At UEG Week in Barcelona, Gilja presented new guidelines on GI ultrasound, now published by the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB). Mélisande Rouger reports**




**A GI ultrasound examination usually starts in the right lower abdomen and often the appendix can be identified. In this image the appendix is shown behind the distal ileum and marked between the two green crosses with a diameter of 0.26 cm. If appendicitis is present, the diameter will increase above 0.6 cm.**

**The EFSUMB** world's first guidelines on gastrointestinal ultrasound (GIUS) contain 19 recommendations on basic technical and clinical methods to perform ultrasound of the GI tract including, for example, how to follow the small intestine, or how to use Doppler.

'Elastography is well established in the breast, prostate, and most importantly the liver, for the diagnosis of hepatitis B and C, and degree of fibrosis and cirrhosis,' explains senior consultant and Professor Odd Helge Gilja, from Haukeland University Hospital, in Bergen, Norway.

'Elastography is fairly new in GI tract, however. We use it to evaluate stiffness of tissue, and indicate if is more fibrotic or inflammatory, for instance in Crohn's disease. Elastography will help us characterise and decide what treatment to chose: anti-inflammatory drugs when the tissue is soft, or to recommend surgery when there is predominant fibrosis.

'Contrast agents are also a rather new addition to GIUS. SonoVue has been used for almost twenty years in Europe, for the liver, pancreas and now GI tract. It gives a better understanding of blood perfusion of the GI tract in various diseases and enables depiction of vasculature or indicates inflammation in the tissue. Furthermore, it's very helpful for abscess detection in and around the intestines.

'Contrast agents and elastography are showing good results, so much that we can now give recommendations, and an increasing number of papers support the use of these techniques, especially contrast agents.

'New GIUS guidelines will be on Crohn's disease and inflammatory bowel disease, and we have four more in the pipeline on GI conditions. It's a really big project. Furthermore, EFSUMB is now updating both the CUES and general elastography guidelines.'

'There are many indications for ultrasound use here, but the main one would be inflammatory bowel disease, Crohn's disease being the most important.

## US and the intestine: sparing invasive colonoscopies

'You can spare a lot of invasive colonoscopies by doing an ultrasound examination instead. It's cheaper, safer, and you can obtain a lot of clinically useful information.

'Doing endoscopy, you only see the surface, but with ultrasound you can see beyond the surface and estimate bowel wall thickness and what is beyond –lymph nodes, for example.

'Avoiding colonoscopy means a more comfortable examination for the patient, and you can do ultrasound beside or on an ambulatory basis.

## A first modality of choice, in some cases

'The choice depends where you are in the world. In some African countries, doctors often use ultrasound directly. In the USA, computed tomography tends to be the most widely used modality, whereas in Europe, the trend is to use ultrasound first in a clinical setting.

'There is a huge benefit in ultrasound in that the clinician can do it immediately, without referring to a radiologist and subsequently having to wait for a report coming one week later. So you can gain a lot of information non-invasively directly at bedside.'

## Bowel ultrasound needs training

'Ultrasound of the GI tract is a little bit more advanced than liver and pancreas ultrasound. Air and bowel movement need specific training. So usually we recommend doing standard training on abdominal ultrasound first, and then progress to more advanced GI training.

The Past-President of EFSUMB and acting chair in the WFUMB Education Committee, **Odd Helge Gilja MD, PhD,** Director and Senior Consultant at National Centre for Ultrasound in Gastroenterology at Haukeland University Hospital, Bergen, Norway, is also a Professor at the University of Bergen. His interests are ultrasound, gastrointestinal (GI) motility, biomechanics of the GI tract, contrast-enhanced ultrasound, perfusion, registration of dynamic image sequences, advanced visualisation, medical imaging, functional dyspepsia, ultrasound microbubbles, targeted diagnosis and treatment. From 2001-07, he presided over the Norwegian Society for Diagnostic Ultrasound in Medicine. He has edited seven books and authored more than 230 scientific papers, as well as 60 popular science publications.

'EFSUMB has ultrasound learning centres (ULCs) all across Europe, which are happy to take beginners, who can come to stay for two to four weeks and have training on ultrasound and specific topics, including GI tract ultrasound. The courses are designed for different levels - doctors need to update their skills constantly, even the most experienced professionals.

'At UEG Week we provided postgraduate ultrasound courses, hands-on training sessions, and offer GI ultrasound specific training under supervision of an expert every day.'

## GIUS training candidates

'Anyone needs training who will use the modality, and that means radiologists, radiographers, surgeons who can specialise in GI and internists – in some countries, internists also treat patients with GI disorders.'

*Contrast enhanced ultrasound delivers diverse benefits*

# Experts present CEUS insights

**In April 2016 CEUS received the USA's FDA approval. This year's RSNA Samsung Symposium 'Contrast-Enhanced Ultrasound (CEUS): Innovations and a Problem-Solving Tool in Clinical Practice' provided an opportunity to take stock. For European Hospital, Professor André Clevert, Director of the Interdisciplinary Centre for Ultrasound at University Hospital Munich, Germany, describes the current state of affairs and ventures a guess regarding the future of this technology.**

**'Today, it's safe to say,** the advantages of CEUS, particularly in paediatrics, are obvious, as Paul Sidhu, Professor of Imaging Sciences at King's College London and President of the British Medical Ultrasound Society, clearly showed in his presentation. Since April 2016, when microbubbles were approved for liver diagnostics in children, the range of diagnostic options has broadened,' Professor Clevert points out. CEUS is important in trauma diagnostics to detect liver injuries or liver haemorrhage; moreover it facilitates the precise description of liver lesions.

The second presentation, by Professor Stephanie Wilson, Clinical Professor of Radiology at the University of Calgary and member of the Diagnostic Imaging Department at Foothills Medical Centre, focused on benign lesions and their changes over time.

'She was able to show in case studies that contrast-enhanced imaging as an additional diagnostic tool offers reliable and fast results,' says Clevert, who adds, 'With CEUS waiting times can be reduced and patients can undergo further diagnostic procedures right after abdominal sonography.'

## Deep insights

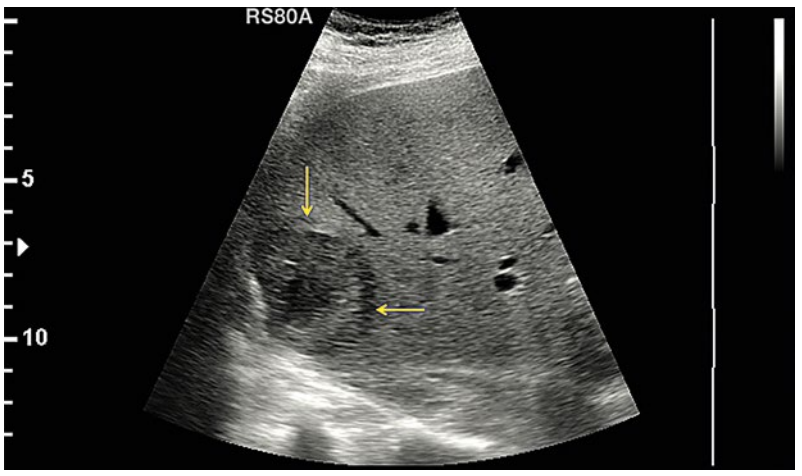
The final presentation on CEUS advantages examined 'the different forms of hepatocellular carcinoma (HCC), from rather rare lesions in the non-cirrhotic liver to mixed HCCs, such as cholangiocarcinoma (CCC), plus HCC. Whilst a CCC, as such, cannot yet be differentiated in ultrasound, a biopsy will tell whether a bile duct carcinoma is present, or a CCC plus HCC,' Professor Clevert explains.

However, CEUS does not only play an important role in HCC diagnosis; it is also extremely helpful in evaluating treatment response, as Professor Clevert points out: 'There are several intervention options for HCC – from transarterial embolisation (TAE) and transarterial chemoembolisation (TACE) to radiofrequency ablation and microwave ablation. All these therapies need adequate follow-up and assessment whether a vital residual tumour is present post-surgery. This is easy to ascertain with CEUS.'

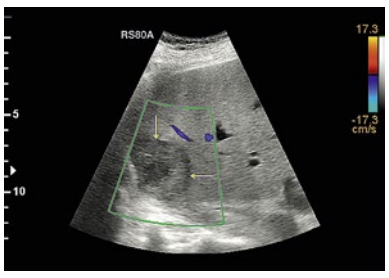
A very rare variant of HCC, the fibrolamellar hepatocellular carcinoma, can occur in young women without coexistent liver disease. This is, as Professor Clevert explains, 'a tumour originating in the liver in younger patients without liver cirrhosis. The tumour usually remains a singular mass in the liver but metastasises to the lymph nodes. The origins of these tumours have not yet been fully researched; genetic disposition cannot be excluded.'

## Above and beyond the liver

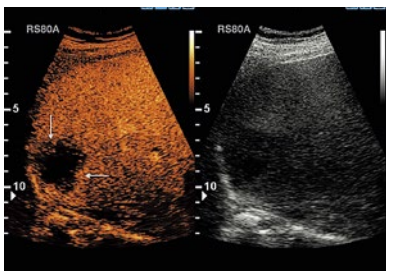
At the RSNA symposium, Professor Vito Cantisani from Policlinico Umberto I, Sapienza University in Rome, Italy, looked at CEUS fields of application beyond the liver, such as the evaluation of plaques. 'Today,' Clevert explains, 'plaque evaluation is done by CT, which, however, cannot confirm vascularisation of plaque. This is where CEUS might come in.' 'Other presenters at the symposium shared their CEUS experience in terms of vessels, kidneys, and other organs. A crucial advantage of CEUS is the fact that, in many cases, changes can only be made visible by administering contrast agents. For example, when an aortic stent has been placed, conventional techniques carry a 30 percent risk that endoleaks are not detected. As far as kidneys are concerned, the diagnosis of kidney cysts is so complex that only contrast media allow precise and fast confirmation of carcinoma or cyst,' Clevert points out.




65-year-old patient after surgical resection of colorectal cancer: B-mode image shows delineated suspicious echo-poor liver lesion (yellow arrows)




Increased vascularisation of the lesion (yellow arrow) is not visible in colour-coded duplex sonography




After administration of contrast medium the liver lesion (white arrow) shows increased wash-out in the portal venous phase. Contrast-medium kinetics indicates liver metastasis

## CEUS – the future

'No doubt, we'll see an expansion of ultrasound diagnostics and a clear focus on multiparametric imaging,' Clevert predicts. 'A major item on our wish list is the display of numeric values in multiparametric imaging for us to be able to detect temporary changes early on and initiate targeted treatment,'

Artificial Intelligence and Machine Learning, major issues at this year's RSNA, present particular challenges for ultrasound, as Clevert knows.

*Extracting valuable information from clinical reports*

# Savana goes data mining

**Artificial intelligence (AI) took centre stage during the Medica Academy sessions. While talks focused on initiatives made in Germany, European Hospital took a look at Spain and spoke with Ignacio Hernández Medrano, a neurologist recently elected as one of the most influential people in healthcare (HC). At just 34 years old, Medrano has already founded two flagship AI projects, one of which enables extraction of valuable data from clinical reports written in free speech: Savana. With a name that echoes fertile lands, the sol-ution may prove very helpful when it comes to mining valuable clinical information.**

Interview: Mélisande Rouger

***What is Savana?***

'As doctors, we have been gathering information from our patients' clinical records for many years. This information has great value, but until now it hasn't really been exploited, because we write our reports in natural language, or free speech. We write in complex semantics and narratives, rather than in a structured way. 'For some years we have been using natural language and linguistics computational processing, so that computers can decode human language. That's the technology used by Google, for instance. 'Savana is the first company that has been able to subspecialise this AI technology to convert free speech contained in clinical records in a database, and to mine this data.'

***What inspired this business idea initially?***

'In our society, we have access to large databases all the time, whether for music, banking, etc. In healthcare, very large quantities of data are being generated, most of which are digital, however, we did not reuse it – which is possible with technology and a bit of organisation. So that's what we did.'

***Is Savana unique?***

'There are many innovative companies in Spain; social entrepreneurship is growing steadily. Technology is a great way to improve people's lives. Savana handles very big amounts of medical information, which very few private or public projects do.

We manage tens of millions of clinical episodes and this makes us very unique. '

***How is big data developing in Spain?***

'Unlike Germany, the UK and the US, Spain did not pave the way for big data use. We need to get on board now and use big data in healthcare. Just as e-banking is becoming banking, e-health is becoming health. The Spanish healthcare system is very strong, but things may change within 10 years if we don't realise that health is becoming digital.'

***Are doctors or healthcare people resisting this?***

'Innovation means realising that you need to get it wrong three or four times before it works. This is very hard to accept in healthcare. Mistakes are badly tolerated, so it's harder for innovation to go further in this sector. That's why big data and digitisation have advanced in other areas, such as banking.

'Nevertheless, no human production generates as much data as a hospital. So big data has an important role to play in healthcare too; and it already does, at the level of drugs and diagnostic or therapeutic algorithms, which improve human capacities.

'It's true that doctors tend to have a conservative attitude, especially regarding their role in society. But, when one realises that powerful algorithms that can improve diagnosis and treatment can be obtained through managing large amounts of data, then everything will fall into place, because patient care improves. If a machine gives what's best to the patient, doctors will follow. And that's not the future: that's right now.'


Source: angellodeco / Shutterstock

***Currently, how many hospitals use Savana?***

'We provide services to around 40 hospitals, so that would be a six million population. We definitely should have more by the end of the year. The more clinical information we have, the better it will be for everyone.

'Outside Spain, we have information from Chile, and contacts with the United Kingdom, the United States and Argentina, and we hope we will expand soon.'

***Are you working on other projects?***

'Yes, I'm working with Mendelian, a company in the United Kingdom, which has developed an online rare disease search engine, built with the aim of increasing diagnostic hit rates. I met the other people behind Mendelian while studying at the Singularity University.

'Rare diseases are complex and take a long time to be diagnosed. There's very little knowledge around these diseases, and our tool offers to speed up the process. Rare diseases associated genes and their existing gene panels are algorithmically matched to phenotypes. Recently we've helped a kid with a rare disease to be diagnosed.'

***What did you learn at the Singularity University?***

'Private companies founded the university eight years ago to promote the impact of positive technology. The school has an annual number of 80 people who all want to improve

**Professor Dirk-André Clevert** began his career at the MRI Diagnostics Institute Westend in the city of his birth, Berlin, Germany, and in the Department for Internal Medicine at the Waldkrankenhaus Gransee. He then worked as a specialist registrar in the Department of Radiology at Passau Hospital for three years. In 2003, he moved to Munich to join the newly founded (2004) Interdisciplinary Centre for Ultrasound at the Grosshadern Campus, University Hospital Munich. The centre coordinates all ultrasound activities in the hospital. As course director and congress president, he organises numerous national and international ultrasound courses and congresses. On the 80th founding anniversary of the Medical Faculty of Tbilisi State Medical University, as head of the Interdisciplinary Ultrasound Centre, the professor was awarded an honorary doctorate.

'Sonography generates huge data volumes since we are dealing with moving images rather than stills. Consequently, in a first step, an image documentation standard has to be defined for the system to be able to learn anything at all. Furthermore the tumour classifications "benign" and "malignant" will not be sufficient to obtain valid results. A lot of work remains to be done!'

Neurologist **Ignacio Hernández Medrano MD** at Ramón y Cajal Hospital in Madrid, Spain, was elected one of the most influential healthcare professionals in 2016 by the specialised press for his work in HC systemic change due to information technology and big data use. He holds several masters in HC management, and he notably sits on the strategic board of Ramón y Cajal HC Research Institute. He gained a bachelor degree at the Singularity University (NASA, Silicon Valley) in 2014 and founded two emerging companies using artificial intelligence: Savana (electronic clinical records processing) and Mendelian (rare disease diagnosis and treatment).

living conditions by using high impact technologies and a positive, exponential approach.

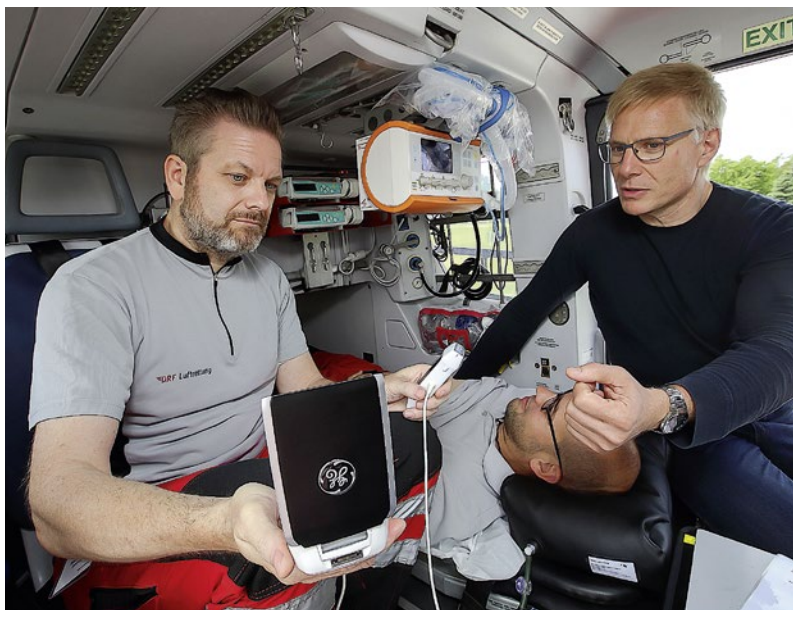
'Technology is changing the lives of many people. Having an exponential approach means that we believe things will go much faster than we expect. This way of thinking changed me; the future is much closer than what we believe. The future will come and it will be for the good; there will be associated problems, of course, but it will improve people's lives.'

Link: https://savanamed.com

*Ultrasound device can now be smartphone size*

# Emergency ultrasound training

**Training is at the heart of the biggest annual fair globally, thanks to the newly introduced Medica Academy sessions, i.e. full-day seminars that deal with practical questions, current techniques and advances in medicine. One of the hot topics tackled by the new format will be emergency ultrasound, with renowned experts such as Dr Wolfgang Heinz from Stuttgart giving hands-on training to use this modality.**



**Dr Heinz training with ultrasound equipment**

**Used in a rescue helicopter after trauma to rule out pneumothorax**

**Report: Mélisande Rouger**

**In 2010 the** German Society for Medical Ultrasound (DEGUM) introduced a curriculum on emergency ultrasound, a basic course for physicians and medical staff with little to none experience in the modality. Seven years later, the program has become a reference in Germany, and about 60 courses are delivered annually all across the country – this year including Medica. Dr Wolfgang Heinz is head of internal medicine at Clinic I, Karl-Olga Hospital GmbH in Stuttgart, and is among the DEGUM course instructors. He chairs the seminar on Tuesday and invites every professional who has to deal with emergency patients to sign up, as ultrasound is central to emergency pathology diagnosis. 'Ultrasound is particularly useful in detecting and differentiating conditions that could easily be missed were it not performed. It is a great tool for emergency physicians. For example in patients who are short of breath, one can differentiate within seconds whether pleural effusions, pulmonary oedema or pneumothorax is the cause. In the pre-hospital setting, ultrasound also helps to bring patients with free intra-abdominal fluid after trauma to the appropriate hospital,' Heinz pointed out.

The course offers both theoretical and practical knowledge, and participants can immediately put in practice what they have learned, and to ask speakers questions.

'Participants train by performing examinations on each other and carrying out ultrasound-guided puncture using models. We teach them how to position the probe and share tips and useful content,' Heinz said.

The course adopts a practical approach and gives insight into protocols such as FAST, eFAST and FEEL, but also focus on various regions of the body – abdomen, thorax, etc.

Emergency ultrasound is a very specific field, therefore Heinz recommends physicians who are used to perform ultrasound examination in their daily practice to attend additional emergency training.

Ultrasound will often be key to support or question initial diagnosis, and the general rule is to see as much as possible. 'It's become our motto as emergency physicians: the more you see, the more you know,' Heinz said. You will definitely see more if you use ultrasound. It can give you core information and help you to use the right therapeutic approach because the diagnosis may be more accurate.'

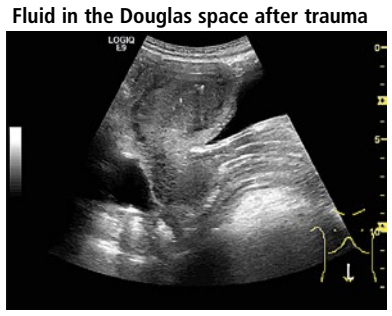
According to Heinz, ultrasound is as mandatory as a laboratory test in an emergency patient – and it is the most available imaging modality across all specialties. 'You just need ultrasound when you meet the patient, and use it as an additional tool to broaden your diagnostic probability.'

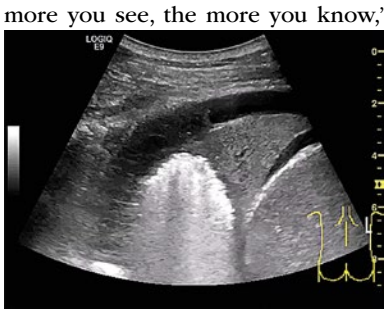
Technology has prompted the widespread use of ultrasound in the emergency setting. Recent developments have squeezed the size of the equipment to smartphone dimensions – and often found ways to insert it directly into a phone.

'Ultrasound devices are so mobile and small that you can bring them anywhere – on a helicopter, submarine, cruise ship, at home, on Mount Kilimanjaro… wherever you want and for any situation. The patient does not have to come to be scanned with a big machine, but we can bring the equipment to the patient,' he said.

Notably, the German Air Rescue (DRF Luftrettung in German) has equipped its helicopter fleet with ultrasound devices. Also, for the past three years, its teams of doctors and paramedics have received training through the DEGUM curriculum.

**Fluid in the Douglas space after trauma**





**Wolfgang Heinz MD** heads internal medicine at Karl-Olga-Krankenhaus GmbH in Stuttgart, Germany, which he joined in 2014. His other interests include gastroenterology, diabetology, palliative care, infectious diseases, intensive care and emergency medicine and flight surgery. He is a DEGUM instructor for the Internal Medicine and Emergency Ultrasound level III course and represents the society's working group on emergency ultrasound.

For Heinz, it's both challenging and motivating to teach such a wide variety of audiences. 'It makes a big difference to teach experienced doctors or paramedics. The latter usually don't have deeper knowledge of human anatomy, so I have to explain things a bit differently.'

The DEGUM syllabus is a two-day training designed for everyone using emergency ultrasound – these may be orthopaedic and trauma surgeons, anaesthesiologists who work within the ICU, internal doctors who work inside the emergency room, people who are underway as emergency physicians or part of a rescue team, paediatric doctors, and those in private practice.

At Medica, participants only receive the first of the two-day training, but may take the second day, which is entirely dedicated to echocardiography, on any other occasion, regardless of where or when.

**Typical emergency situation in Germany**

*AI, Big Data, wearables, apps, robotics and VR*

# E-health developments in Spain

**Esalud, the Spanish annual event, took place in Madrid at the end of November with 200 on-site participants, a live streaming audience and over 55 million viewers on twitter. European Hospital correspondent Mélisande Rouger spoke with Carlos Mateos, Vice president of the Spanish E-health Researchers Association, who organised the conference, to assess the latest advances in e-health projects across the peninsula.**

**Highlights** – 'The meeting featured the second consensus on internet-based health information. Healthcare professionals, journalists and patients worked together on ways to improve the quality of information available online, and confront issues such as rumours or erroneous information,' explained Carlos Mateos, Vice president of the Spanish E-health Researchers Association.

'We were happy to welcome once again a great variety of health-related institutions – scientific societies, patient organisations, professional colleges, management associations and healthcare authorities.

'Our session tackled advances in artificial intelligence, Big Data, wearable devices, applications, robotics and virtual reality.

'We also offered a space for entrepreneurs to show their ideas and start networking with potential investors and companies. A lot of interesting solutions are now being developed that can really improve healthcare (HC). The main problem remains that the adoption curve for every technology is stagnant.'

## Healthcare gamification

Gamification – using aspects of game playing, i.e. point scoring, competition with others, rules, in marketing and in this case – to educate and rehabilitate, has definitely

Initiatives involving virtual reality focus on updating healthcare knowledge, phobia treatment and motor rehabilitation

consolidated. When we organised our first conference on videogames use in healthcare in 2014, most HC professionals and a significant amount of companies had no idea what gamification was. Now it is part of healthcare training and education programs.

'Many applications aiming at improving treatment adhesion and raising awareness of healthy habits also use gamification, and so do most wearable and rehabilitation devices.

'A number of projects also use gamification to rehabilitate patients who suffer from neurological pathologies. I'm thinking of CicerOn, an initiative led by the research chair in accessible technologies at the University Centre for Technology and Digital Art (U-Tad), Universia Foundation and IT company Indra. CicerOn helps patients with Asperger's syndrome to train for public presentations and social interactions.'

## Big Data and Spanish healthcare

'Healthcare very much lags behind industries like banking or finance, which really integrated Big Data. Healthcare insurance companies and hospitals are using large amounts of data to improve their profits and knowledge of patients and HC professionals' behaviour, but much more could be done.

'One of the big issues is data safety, which is being increasingly threatened by massive cyber attacks and the system's many vulnerabilities.

'In terms of disease prediction in Spain, we have interesting initiatives that use Big Data to locate bloodmobiles, detect genes linked to disease and even predict disease risk by sending a daily picture, the focus of start-up Scan4Us.'

## Virtual and augmented reality

'Most initiatives involving virtual reality (VR) and augmented reality (AR) aim to update healthcare knowledge, but many now also focus on phobia treatment and motor rehabilitation.

'For example, the Spanish company Psious uses VR to treat fear of flying, driving or speaking in public. The Foren Centre in Madrid uses neurorehabilitation based on VR and has already achieved results in patients with disease or trauma induced motor lesions.'

## Social media challenges in healthcare

'The main challenge for professionals is to find value in training and communication with other specialists, and to improve communication with the patient. Many say they lack the time to do so, but the efficient use of social media enables time saving and improved work and business perspectives.

'Patients need to make themselves heard. Some associations receive a lot of echo on all their activities because they are very present on social media, while others remain invisible to the public eye and only once in a while publish something.'

## Wearables

'Smart materials are becoming basic to control risk, not only in cardiac patients in a non-intrusive way, but also in healthy patients who practice sports and want to avoid a big scare.'

## Chatbots as a solution to Google searches

'Chatbots use is taking off and their pertinence will grow, along with the number of interactions. They will be key in the future,' Mateos predicts, 'to deliver first assistance and internet-based information.'

With over 20 years of journalism experience specialising in healthcare management, **Carlos Mateos** is Vice President of the Spanish E-health Researchers Association and director of Com Salud, a communication agency focused on healthcare. The agency also organises the National Congresses of Health Games, Wearables and Big Data in Healthcare.

*Creating a paperless healthcare facility*

# 'We are building the digital DNA of the organisation'

**Report: Mark Nicholls**

**The NHS in the UK** aims to be paperless by 2020. While some observers may regard this timescale as ambitious, other NHS trusts are well advanced in the transition toward a fully digital environment.

One leader in the field, Oxford University Hospitals NHS Foundation Trust, is about to go live with its first fully digital ward and also in the process of making all nursing documentation digital across the entire organisation and then to make the remainder of medical documentation digital, with a target to be paperless within two years.

Yet to reach this stage of 'digital maturity', the trust's Chief Information and Digital Officer Peter Knight acknowledges it has been a lengthy journey with a number of people driving the project with leadership and determination over the past few years.

Speaking about what it takes to be a truly digital healthcare facility, he said: 'You also need a vision to where you want to get to, but that vision will not necessarily stay static because technology develops and moves rapidly. Part of the focus is to make sure you keep up to date with technology and that is really important in the cyber security space, for example. What you have to remember is that you are building the digital DNA of the organisation.'

The Oxford Trust aims to become paperless within two years

Establishing a patient administration system is a critical first step and then building a clinically-based delivery point and collection of clinical data from that. Oxford University Hospitals has already seen digitisation implemented in the emergency department and a neuro intensive care unit that is completely paperless, with all documentation online with the electronic patient record (EPR). 'We have built clinical functionality - being able to order medication and tests are fundamental to that model of delivery,' Knight explained, adding that an important facet is to offer positive apps that clinicians can use intuitively.

Additionally, the transition to digital has population health opportunities and the chance to bring clinical records together - whether from primary, secondary or community care - into the core system to see the longitudinal record of the patient. From that, there are population management opportunities and using the data to manage conditions – such as COPD or diabetes – more effectively in the community, with a preventive and well-being agenda and lightening pressure on the hospital system.

Other benefits are in managing the organisation and flow of patients and enabling patients to access the system and their records, book appointments, talk to clinical teams and record information such as a pre-operative assessment or post-operative diaries.

With clinicians able to access records and imagery, from wherever they are, patients gain a faster, better service.

However, the Chief Information and Digital Officer stressed the importance of guarding against 'overloading' clinicians and staff with digital data as they transition.

With the digital transition, cyber security remains a critical issue, especially after some NHS units were among organisations affected in the global cyber attack last May. 'When that attack on the NHS occurred,' said Knight, 'we survived because we take cyber security seriously. We protect our borders with the latest technology; our patch management strategy is as automated as possible and we respond as soon as we are alerted; and we are good at communicating to our staff about things like not opening emails which look "dodgy", but we can never be complacent.'

With the Oxford University Hospitals NHS Trust aiming to become paperless within two years, it is already moving towards most referrals into hospital from clinicians, patients and primary care, being done electronically. However, that goal is also dependent on the rate at which partner organisations work towards being fully digital.

As hospitals and health systems across the UK and Europe work towards fully digital, Knight has a clear message for them: 'Make digital the core of your business.

'In essence,' he added, 'it will enable you to manage your patients and clinical risks more effectively, it will enable you to deliver better services and you can use real data to manage your business rather than rely on anecdote.'

Before joining the United Kingdom's Department of Health in 2007, **Peter Knight** headed the introduction of Cerner at the Winchester and Eastleigh National Health Trust, among his other operational and board responsibilities. He became Deputy Director at the Department of Health for Research Contracting, Information Intelligence and Stakeholder Engagement, working under Professor Dame Sally Davies, the Chief Medical Officer, until 2016. He is now Chief Information and Digital Officer and an Executive Director of Oxford University Hospitals NHS Foundation Trust, and a Senior Fellow of Health Informatics at the Nuffield Department of Population Health, University of Oxford.

# Knowledge dissemination is key to defeating cancer, says renowned expert

**Half of cancers can be avoided if institutions would exchange knowledge, according to Joxel García, executive director of the University of Texas MD Anderson Cancer Center in Houston, who opened the Center's meeting in Madrid in October 2016.**

**Report: Mélisande Rouger**

From left: Dr Joseph Khoury with Dr Juan Fernando García García MD, from the Anderson Cancer Center Madrid and Joxel García, MD Anderson Cancer Center Houston.

**Technology has progressed** enormously and there has never been that much knowledge of cancer to prevent it and find treatment tools.

'We can prevent 50% of cancers approximately; and if we can't do that, we can at least detect them in stage 1 or 2 instead of 3 or 4,' Garcia stated in his inaugural lecture. But, he added, medicine is heterogeneous and its focus not well adjusted. 'The current clinical care model is episodic, reactionary and very expensive; it varies from country to country. We concentrate on who finds the next cure and what is going to be the next silver bullet. In 20-30 years from now I think we're going to look back and say: you guys did it wrong.'

For instance, health professionals know the cost of disease but do not have a value for a person's health. 'In population healthcare we can only talk of pathology; it's a pathology-centric process. We have to combine the knowledge of scientists to be able to identify the real diagnosis and have people like me and others find a way to prevent that cancer from happening.'

One way to do so is for healthcare providers to use models based on quality evidence-based decision support, he argued.

MD Anderson's Moon Shots program is an initiative that uses a transdisciplinary approach to speed up the development of new treatments, diagnostic methods and prevention programs from scientific discoveries. The centre, which collaborates with community hospitals and health systems in the USA and has a local branch in Madrid, has 13 moon shots, each dedicated to a particular cancer area.

'If the knowledge we have today was applied effectively, it would reduce cancer mortality within the next five to 10 years of initiation of a moon shot project,' García said quoting Ronald DePinho, president of MD Anderson Cancer Center. 'What he meant is that our goal is to do what currently takes eight to 10 years in three to five years.'

The centre's Moon Shots program notably inspired former US President Barack Obama, who announced a national cancer moon shot to cure cancer.

On the US level the centre has managed to influence change in some states' legislation regarding minors' protection, for instance by forbidding youngsters' access to tanning beds, a known risk factor for melanoma in younger populations.

This remains a significant challenge in the US, according to García. 'We have a trillion dollar system which is very ineffective; there's a huge disparity of knowledge, one of which is among physicians.'

One of the organisation's aims is to help spread knowledge to non-specialised centres through their network.

The centre also cooperates with the WHO on prevention and control, and provides community based services and teleconsulting in nutrition, exercise, smoking, prevention, UV protection and vaccination at various sites across the world.

One of the main issues in cancer research is knowledge dissemination. 'There's a lot of knowledge in a lot of pockets, but they do not exchange intelligence between them. Why don't we share data and information?' he suggested.

A step in that direction, and a currently highly discussed idea in population health, is to open clinical trials not only to people who can meet the criteria, but also to people who might have other diseases.

Typically a medication approved by the FDA to go to a clinical trial comes out successfully in only two to three percent of patients who actually qualified for that trial, Garcia pointed out.

'As soon as the drug goes into the market it has actually never been tested in people with asthma, diabetes or other chronic diseases. And then the drug fails and comes out of the market, and you've lost a billion dollars in research and 20 years of work.'

MD Anderson also plans to narrow the gap between providers to increase the number of available phenotypes. The centre's US network tries to identify locations that have other genomic pools to identify more mutations and see how those are affected in terms of phenotypes per se.

Additionally, the institution is working to create a digital platform for second opinion pathologists, because those specialists are cruelly lacking in many areas, including Africa, Asia, parts of Latin America and Eastern Europe, and the USA. 'Several years ago we had areas in Connecticut where the diagnosis would come from a general surgeon. Endometriosis was diagnosed as ovarian carcinoma and a patient would have had three to four different chemotherapies, she was cured after six months… but she never had cancer. This should not happen in a community.'

Having predictive models comprising people's genotypes and identifying which factors can amplify cancer risk, such as living area, are the future of medicine, not only in cancer but also chronic diseases, García believes.

Screening services will have to adapt to the needs of a particular person, unlike the 'utopic idea that people should have mammograms at this age, or a PSA test at this time. A lot of biomarkers will help and change the way we practice medicine,' he believes.

However policy makers must back up institutions so that communities can have more access to up-to-date healthcare.

A former four-star admiral in the USA's Public Health Service Commissioned Corps and US assistant secretary for health in that service, since 2013 **Dr Joxel García** has been Executive Director of the MD Anderson Cancer Control and Prevention Platform in Houston, Texas, USA. He is also a member of the leadership team of the MD Anderson Moon Shots program. Prior to these endeavours, he served as president and dean at the Ponce School of Medicine and Health Sciences in Puerto Rico.

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# Solid IT hardware and communication

**When Taiwan-based** Adlink acquired Penta, the buyer benefited from 20 year's experience in design and hardware manufacturing. Today, Adlink provides state-of-the-art computing products such as advanced TCA processor blades and platforms, compact PCI/PlusIO, VPX blades, industrial SBCs, motherboards and chassis, plus embedded flash storage, computer-on-modules, rugged small form factor SBCs & systems, fan-less embedded computer, wireless internet gateways, and SEMA cloud. The firm's IMPS product lines include industrial mobile handheld computers, smart panels, smart touch computers, industrial & panel PCs, medical PCs & display.

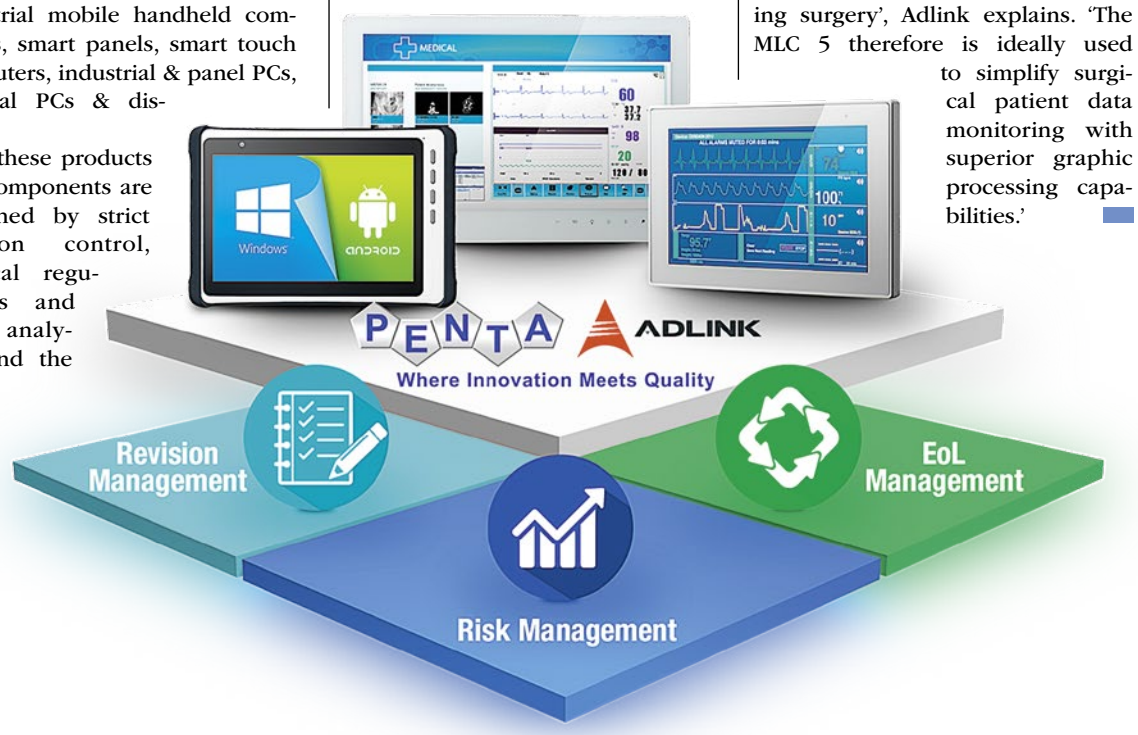
All these products and components are governed by strict revision control, medical regulations and risk analysis, and the firm emphasises that it also ensures support for customers who want to integrate the medical product solutions into their own medical systems.

'Adlink products also support multiple operating systems and include comprehensive and easy-to-use software packages and services,' the manufacturer confirms.

## Medical panel computers

The medical panel computers and monitors have been designed with optimum viewing capabilities and hygienic fully-sealed and easily cleanable housings, suitable for patient vital sign monitoring, nursing care, clinical diagnosis, PACS, anaesthesia monitoring and OR documentation.

'The MLC 5 medical panel computer is designed for digitally integrated operating theatres to enable easy access to PACS images, EHRS and other relevant patient data. The device allows surgeons to manage the patient's vital parameters and other critical information during surgery', Adlink explains. 'The MLC 5 therefore is ideally used to simplify surgical patient data monitoring with superior graphic processing capabilities.'



*A brief history of mass spectrome*

# Analytics meets diagnostics

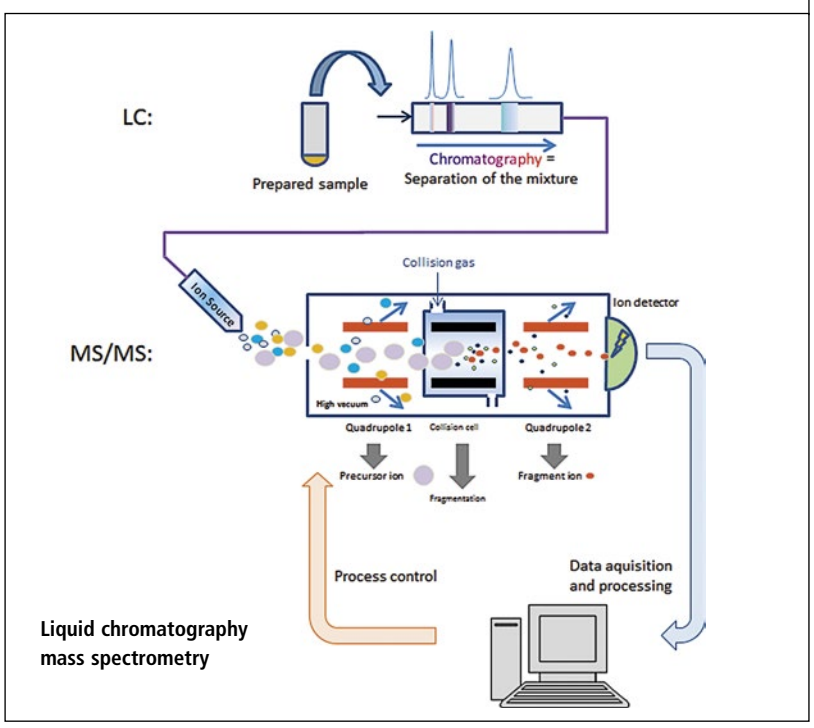
**Report: Walter Depner**

**Up to the early** 16th century, essentially medical diagnostics was limited to uroscopy – the observation of a urine sample in a uroscopy flask with a candle providing light.

In a visual examination the doctor would determine the colour of the urine as well as cloudiness and precipitates, followed by a smell and taste test. The information he gathered provided the basis of his diagnosis.

One hundred years later, the first microscopes were developed to examine insects in 60x magnification.

Around 1650, the devices had become powerful enough for scientists in the Netherlands to discover red blood cells. From then on the development of technical devices and instruments boomed. While we can assume this evolution has not yet reached its pinnacle, in the 18th and 19th centuries it did take very different routes in the life sciences (medicine, chemistry, biology): in chemistry and medicine, a series of distinct analysers were invented. Only in the 1960s, some clever people thought it high time to bind again what had been strictly divided by convention.



Liquid chromatography mass spectrometry


Courtesy of ThermoFischer

Combining chromatography instruments and mass spectrometers, for instance, began with the sole purpose of chemical analysis. Only later it was recognised that this fused technology yields excellent results in medical diagnostics.

## Pioneer Herbert Keller

A major European trailblazer of laboratory analytics, clinical chemistry and related disciplines was Professor Herbert Keller MD PhD, at Kantonspital St. Gallen, Switzerland. In a presentation 'Artificial Intelligence' given in 1990 at a symposium in honour of his 65th birthday, Keller underlined a 'very desirable cooperation' between chemistry and medicine, 'wherever such a co-operation makes sense'.

In the 1950s, Keller had completed his chemistry and medical studies with a double doctorate. In the 1970s and 1980s, he served as President first of the German Society for Laboratory Medicine and subsequently of the German Society for Clinical Chemistry.

More than fifty years ago, he (and a few others) realised the cross-fertilisation potential of interdisciplinary work, and the fusion of clinical chemistry and medical diagnostics was to become one of his lifelong projects.

Unfortunately, he did not live to see his endeavours come to fruition in 2003. While he did witness the


Courtesy of Sciex

*Manufacturers vs. bureaucracy*

# 'We will master this problem'

**Report: Lena Petzold**

Norms and directives are the backbone of medical devices manufacture. Frequent updates keep them current, but also often create unforeseen problems, especially for smaller and medium-size companies, because the bureaucracy is rarely considered.

No exception to this, the EU IVD directive, issued in May 2017, contains new definitions of requirements for in-vitro diagnostics. The new version stipulates more extensive documentation requirements than before. 'This creates significant, additional expenditure for manufacturers,' says Christian Hötzl, founder of Teco Medical Instruments, Production + Trading in Neufahrn, Germany.

He knows this from his own experience with ISO 13485, a standard that governs requirements for medical products manufacture – its latest version came into force in 2016.

'We are a company with 20 employees, which offers products and solutions for blood tests,' Hötzl explains. 'We have customers worldwide. Prior to the introduction of the standard, it was possible for an employee appointed as a quality management representative to take on the documentation requirements, i.e. the drawing up of protocols, writing of product descriptions and defining of workflows. The extension of the obligations has made it nigh on impossible for all the necessary steps to be managed by one person alone, especially as the risk assessment now includes the manufacture.'

This means that a comprehensive risk analysis must be carried out during the production process. 'As a manufacturer we obviously always try to optimise processes and make them safe; but now we must document in writing that we have analysed and, if necessary, remove the possible risks involved in each and every step of the procedure.'

## Critical market surveillance obligations

One particularly critical point is the expansion of the market surveillance obligations. 'Manufacturers must document that they scrutinise the market extensively and that they react to any potential risks,' Hötzl explains. Companies are asked to publish any notifiable errors without delay. These are published in central databases such as the BfArM (Federal Institute for Drugs and Medical Devices) portal.

'We have to check these notifications and, if problems are reported for products in similar areas, such as competitors' products in the field of coagulation diagnostics, we need to investigate without delay if these problems can potentially also occur with our products. If this is the case we need to take the necessary countermeasures at once, otherwise we are obliged to provide precautions to ensure that the problem cannot even arise.' In the worst case, this can affect an entire series of devices and may necessitate a product recall. As we know from the automotive industry, this can quickly assume alarming proportions. However, this is not the only reason why accurate operation is a top priority. 'Coagulation diagnostics is an extremely sensitive field because incorrect treatment with anticoagulants can be life-threatening,' he warns.

The manufacturers' responsibility not only extends to accurate operation. According to the standards, all manufacturers must take precautions to ensure that their products cannot predictably be misused. 'Exactly what this means is not clearly defined in the standard, forcing manufacturers to comprehensively safeguard themselves in all directions,' Hötzl emphasises. This includes the design of devices with long-term stability in mind. 'We carry out extensive life-time measurements and test and record the stability of the measurement optics, the heaters and all other parts potentially prone to wear and tear,' Hötzl explains. 'However, it's even more important to maintain good working relationships with distributors and customers to find out exactly how the products are being used on a day to day basis. Workflow differs from laboratory to laboratory, so it's therefore essential to maintain communication and find out about any potential sources of error at an early stage.'


## Preventing anomalous use

However, even this is not enough to guard against misuse. 'We are also required to prevent so-called anomalous use. This includes, for instance, the use of cuvettes that are not licensed. 'Our quality cuvettes, devices and other consumer and wear parts are subject to the strictest quality standards. Products from manufacturers that are not licensed can be of lower quality and can block the devices or even falsify measurement results. Although we are not responsible for the potential use of any third-party cuvettes we can ultimately be made liable.

'From a legal perspective, as soon as we become aware of the existence of any such problematic cuvettes

early days of tandem mass spectrometry (LC-MS/MS), the combination of liquid chromatography (LC) and two mass analysers in mass spectrometry (MS/MS), he passed away before this technology conquered clinical routine.

## High-performance tandem mass spectrometry

The technique entails combining chromatographic separation with subsequent highly specific and sensitive detection.

One crucial advantage of this method is that, depending on the method, several values can be determined in one run. Other widely used methods, such as immunoassays (ELISA, RIA), photometry or conventional liquid chromatography (HPLC), are all highly specific and do not possess the same high degree of substrate specificity as LC-MS/MS. When used properly, the capital expense is quickly amortised, since high-performance analytical methods can be established quickly with low operating costs for supplies and chemicals. Efficiency can be further increased by using fast UHPLC separation and commercially available open automatisation platforms.

## Newborn screening and drug monitoring

What are the current and future fields of application of tandem mass spectrometry? According to Dr Matthias Weber, LaborDiagnostik, Karlsruhe, Germany (matthias.weber@labor-karlsruhe.de), newborn screening for metabolic disorders is important and indeed has been mandatory since 2005 because its long-term benefit EBM is well established. Similarly, LC-MS/MS has long been considered gold standard and indispensable in therapeutic drug monitoring and drug analytics.

A more recent field of application is steroid analytics (e.g. cortisol, testosterone, 17-hydroxy-progesterone). Since cross-reactions, a well-known problem with the routinely used immunoassays, do not occur in tandem mass spectrometry, this procedure yields much better results and unambiguous clinically relevant information. LC-MS/MS is also useful for proteomic, metabolomic and steroid profiling in clinical routine and will surely enable the clinician to arrive not only at a faster but a more precise diagnosis.

## Increased precision

On possible future applications in analytics, Weber said, 'We already use conventional LC-MS/MS systems routinely for qualitative questions such as haemoglobin differentiation, thus closing an underreported diagnostic gap. Moreover, a number of tumour markers and panels were described that can be detected with high sensitivity and specificity in plasma or urine with LC-MS/MS. Synthetic peptides and metabolites, even in stable isotope-labelled forms, are easily available today, which is a precondition for widespread use of these methods in the short term. In my opinion, the increased use of mass spectrometry methods will significantly increase diagnostic precision.'

**Dr Matthias Weber** is a Consultant in Laboratory Medicine and General Medicine, as well as Clinical Mass Spectrometry in Karlsruhe, Germany.

**Christian Hötzl** is founder and shareholder of Teco Medical Instruments, Production + Trading. Following an apprenticeship as a physics laboratory technician, he completed a degree course in medical technology at the Medical Technical Academy Esslingen, Germany. For the next six years, he worked for a medical devices manufacturer in Munich, Germany, initially as international head of service and later entered sales and development, his last role being acting production manager for coagulation analysers. In 1990, by buying the coagulation division, he founded Teco GmbH and has since successfully focused on worldwide distribution of his products.

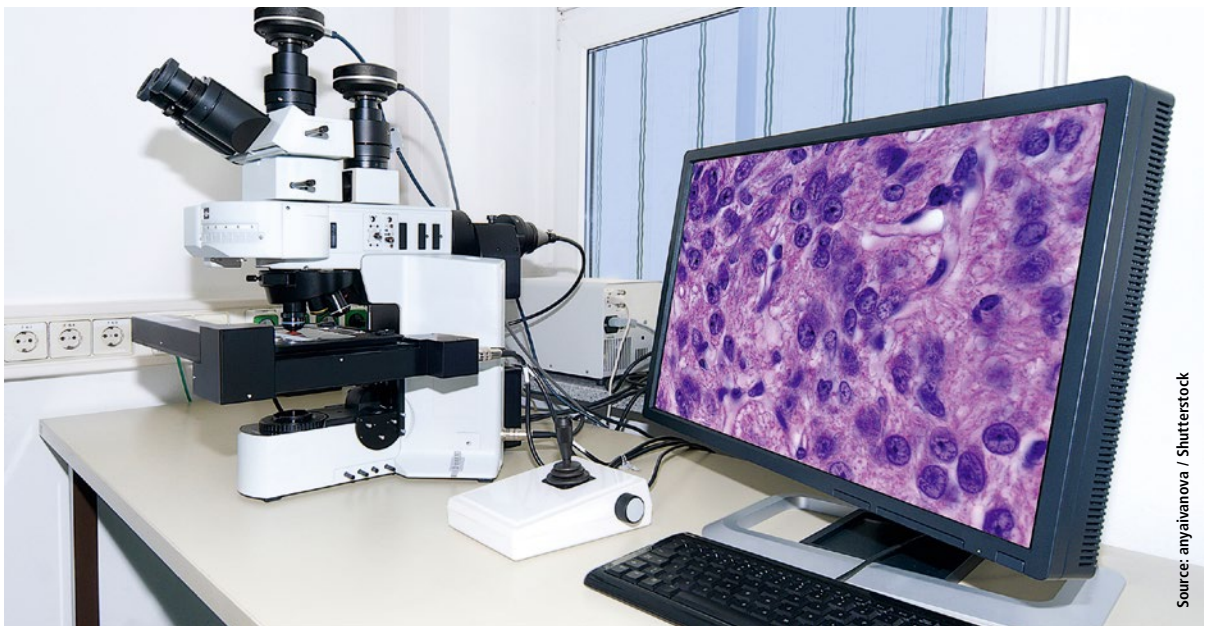
we may be accused of not having done enough against any predictable anomalous use.'

Therefore, the company has gone on the offensive and has developed a closed system for its own products. 'Our devices only allow the use of certified, original cuvettes. After delivery to the end user these are scanned via a barcode system, or an RFID-tag. This identification prevents the use of other products.'

Risk analysis and safeguarding against any misuse may amount to a heavy workload, but Hötzl is optimistic. 'We have more than twenty-five years' experience in the market and will master this, despite all the bureaucracy.'

*Capital investment and IT capacity are hurdles*

# UK uptake increases in digital pathology



Source: anyaivanova / Shutterstock

**Digital pathology is already making a difference in areas of training, education and revalidation**

**Report: Mark Nicholls**

**Professor Jo Martin**, the newly-appointed President of the Royal College of Pathologists in the United Kingdom, believes the National Health Service (NHS) is on the brink of embracing digital pathology more widely. A number of UK laboratories, he explained, are adopting digital pathology in histopathology – in line with some labs in Sweden and Holland, where it has become routine – and the benefits to clinicians and patients in increased efficiency, quicker results, and flexibility are ever more apparent.

However, there remain investment challenges, particularly at a time when the NHS is facing severe financial pressures. 'I think the barriers to wide-scale adoption are largely around capital investment and IT capacity,' Martin pointed out. 'However, I think there is an increasing recognition that digital pathology – with the workforce issues we have in pathology and histopathology in particular – will help us work in a more effective way.'

Challenges also lay in integration with the electronic health record and laboratory information management systems and having the capacity to implement such major change. Yet, she also said digital pathology offers 'huge advantages' in the way it will improve workflow, meaning pathologists can work remotely and share slides and information digitally – as opposed to current glass slides – as they make a diagnosis or seek a second opinion for patients and deliver quicker results for patients.

Additionally, it offers flexibility and more efficient working, routine quality assessment, quality assurance and training opportunities.

A keynote speaker at the Digital Pathology Congress in London with the presentation 'Digital pathology – making a difference', Jo Martin added: 'There is also the integration of digital pathology with molecular pathology and genetics, in the way that we are already doing for integrated reporting, for example in haematological oncology where histopathologists are already using genetic data, and flow cytometry data, haematological data and morphological data and integrating those into one report. Combining the image based potential with the other elements of the genetic data is very important.' Martin also pointed to the potential for the integration of machine learning and artificial intelligence, and how validated algorithms can cut down on routine workloads and save time, such as with the ability to count mitoses per high power field.

Digital pathology is already making a difference, she pointed out, in areas of training, education and revalidation, where pathologists can share digital slides and make diagnosis and comparisons as part of a learning and education process, such as through the EQA (External Quality Assessment) process.

As for future trends and opportunities she continued: 'The potential is huge for sharing, learning for more adaptable training programmes, and for more flexible working. It will help in retaining people in the workforce longer, enabling more flexible working, and those returning to work and in creating the potential for resilience between sites.'

The Royal College of Pathologists (RCPath) is working actively to encourage and support the expansion of digital pathology and expertise in the field, along with a range of other measures to help make working pathologists lives easier at a time of great workload pressure.

'We have issued guidelines about the use of digital pathology and will continue to look at professional standards in relation to the use of digital pathology,' Martin added. 'The curriculum requirements are constantly being reviewed, not just for digital pathology but also for information technology, and we are looking at training modules that will support that.' During her coming three-year tenure as RCPath President, she is keen to raise the profile of the profession, increase its influence with other national bodies, and further highlight the levels of expertise within the discipline of digital pathology.

The other element is to ensure that the organisation continues to be active in research and development, she said. 'Digital pathology has come about in huge part through the activities of pathologists; we have very skilled practitioners working with industry to create these ground-breaking products and this is happening across pathology.

'I want to raise awareness of the R&D and innovation that is going on throughout the profession and show that, as pathologists, we are not just stuck in labs, we are out there preventing, monitoring and in many cases helping to treat disease through new drug development and new technology development.'

**Professor Jo Martin**, who became President of the UK's Royal College of Pathologists in November, is a practising histopathologist, specialising in renal pathology and gastro-intestinal neuro-muscular disease at the Royal London Hospital and is Director of Academic Health Sciences, Barts Health NHS Trust. As Professor of Pathology at Queen Mary University of London, her research interests are in gastro-intestinal and neuro-muscular disease of the gut as well as drug development.



*A new display and calibration kit*

# Accurate colour augments pathology diagnostics

**Digital pathology** places particularly high demands on image quality and thus on monitors. Especially the exact colour rendering is a challenge – no other discipline needs such precision for a reliable diagnosis. To that end, following 'intensive research and development', JVC Kenwood has launched the JD-C240, a 24.1-inch colour monitor. 'We are drawing on many years of experience in the professional video sector, especially regarding colour calibration and adjustment,' Marcel Herrmann, Marketing Manager for Totoku at JVC Kenwood, pointed out.

The JD-C240 has some new, innovative technologies, including contrast enhancement, which was developed specifically for imaging in pathology. Usually, such technologies only improve the contrast and the dynamics, but this leads to a less realistic image reproduction, the company points out. 'To avoid this, we have taken a completely new approach,' Herrmann says. 'The contrast enhancement recognises transitions like structures and improves them. The rest of the picture remains untouched.'

The colour enhancement gives the user full control over colour reproduction. So far, only red, green and blue can be adjusted. 'With our monitor, users can select any colour from RGB or CMYK and adjust the colour saturation, hue and brightness,' Herrmann explains. 'In addition, a tolerance for the settings can be specified for each channel.'

## Same colour impression on all displays

However, to take full advantage of the monitor's possibilities regular calibration is important – particularly for pathology the display must reproduce unadulterated colours. It is important that all monitors within a workflow display the characteristics the same. 'All of this is supported by our new calibration kit CAL016 on the JD-C240,' Herrmann points out. 'For the first time, we'll be able to profile all displays within a hospital and thus ensure a uniform image impression across all departments.'

The CAL016 also supports the 3-D Look Up Table of the JVC JD-C240.

**Colour enhancement gives the user full control over colour reproduction on the monitor**