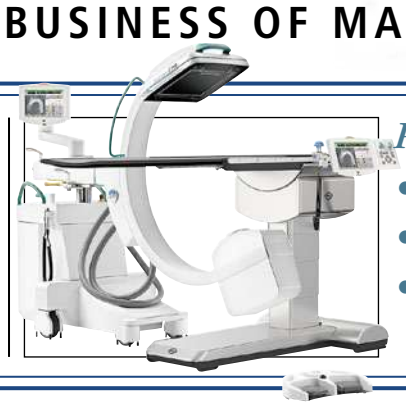
VOL 28 ISSUE 6/19 • December/January 2019/20

# EUROPEAN HOSPITAL

THE EUROPEAN FORUM FOR THOSE IN THE BUSINESS OF MAKING HEALTHCARE WORK







# Cancer care: 2035

## The future has begun - and it is multi-disciplinary

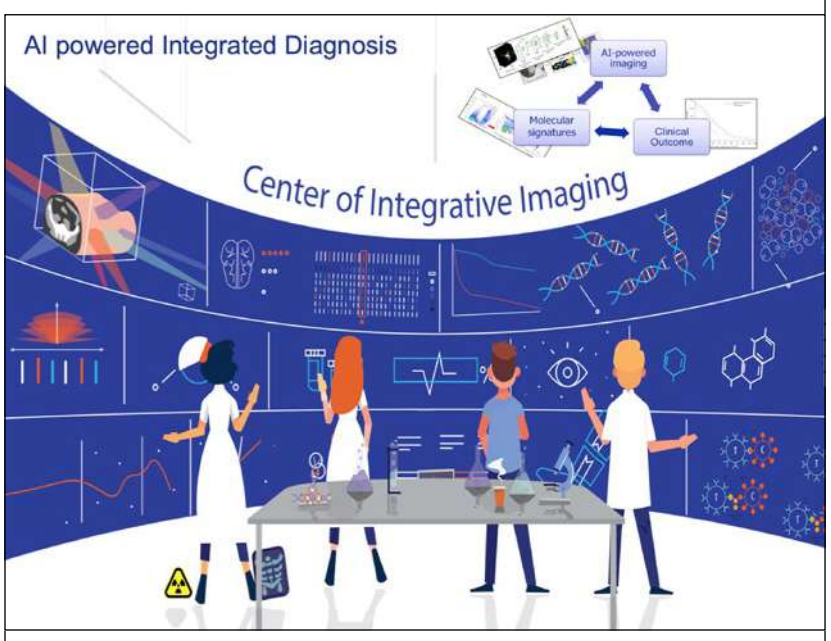
**Report: Mark Nicholls**

**An enthralling insight** into the care that could be offered to cancer patients of the future was presented by cancer imaging expert Professor Regina Beets-Tan during her a keynote presentation at the recent British Institute of Radiology congress.

In the session 'Oncologic imaging: Future perspectives', the professor outlined what a Multi-Disciplinary Team (MDT) of the future – a team in 2035 – would look like in an era where cancer care will centre on patients, precision medicine, screening and detection of early tumours, minimally-invasive treatment, targeted therapies and imaging, and prolonged survival for patients with metastatic disease.

Treatment, she suggests, will feature image-guided precision radiotherapy, surgery, and effective targeted therapies and immunotherapy.

Beets-Tan predicts that the MDT meeting of 2035 would consist of the treating physicians and interventional radiologist along with other diagnostic specialists, to include a geneticist, pathologist, and computer scientist. Such a team will deliver an integrated approach to diagnosis and an integrated solution to a clinical question. 'The radiologist will be a full arm of his clinical partners and will be working side by side to give best care to the patient, who will be engaged in the treatment decision-making after the risks and benefits had been explained,' she envisions. 'Minimally-invasive treatment and organ-preserving treatment, which will improve quality of life, will become part of the spectrum of treatment options because we will see more complete responses to the highly-effective local and targeted therapies.'




**The concept of integrative diagnosis: a radiologist, molecular pathologist, data scientist and geneticist working together to decide on an integrated solution to a clinical diagnostic question**

The radiologist will work together with computer scientists and software engineers to validate Artificial Intelligence (AI) work on high volume, non-complex diagnosis, leaving the radiologist with more time to focus on complex cases and interact closely with clinicians.

The interventional radiologist and surgeon will work closely together in image-guided intervention and surgery to provide good local control with less collateral damage. 'This paradigm shift in personalised medicine will be a move from tissue to molecular risk profiles; from imaging the tumour to imaging the tumour micro-environment,' she added. 'Mutation in genes are the drivers of cancer growth and that is what you want to target. Mutational burden and molecular profiles of tumours become the key factor in cancer treatment.'

Beets-Tan also discussed the potential of AI to prevent over-treatment with immunotherapy. Costs of immunotherapy and risk of toxicity with combination therapy are high, so AI-powered accurate prediction models of outcome will play an important role.

### Fast AI prediction

'Our work in radiomics has shown that AI can predict response to anti-PD-1 at first follow-up. First studies have shown that tracer imaging has the potential to non-invasively map the entire tumour heterogeneity and its response to treatment, which cannot be captured by a single biopsy of only one lesion.

**Regina Beets-Tan** is Professor of Radiology at the University of Maastricht and the University of Southern Denmark, and also chairs the department of radiology at The Netherlands Cancer Institute in Amsterdam. Her clinical expertise is in oncologic and abdominal imaging with a research interest in MR imaging of cancer and specifically colorectal cancer, image-guided interventional oncology and AI. She is 2nd Vice President of the European Society of Radiology, Past President of the European Society of Oncologic Imaging and President of the European Society of Gastrointestinal and Abdominal Radiology. Beets-Tan is also a member of the EU mission board for cancer.

'We need to keep searching for non-invasive advanced tools that can drive precision,' Beets-Tan concluded. 'Borders between disciplines will fade; it will be about patients and patient-shared decision-making and the best outcome. We will have a role as a radiologist that is different from now; we are going to combine our skills in technology with our knowledge of treatment. It is an exciting future for those working in oncology because the new beginning has just begun.'

The treatment possibilities she outlined are the future, she stressed but, in 2035, 'the present' is a mere 15 years away.

*The most advanced digital model of a human neuron*

# Discovered: what makes us human

**A multinational and multidisciplinary team of researchers has developed the most advanced digital model of a human pyramidal neuron, with which they have been able to reveal some of the most fundamental differences between human and rodent brains and help to explain our superior cognition and memory – in essence, what makes us human.**

**Report: Callan Emery**

**Their work** – the most comprehensive, experimentally-based, modelling study of any human neuron – has been published in *Frontiers in Cellular Neuroscience*.

The researchers say this work 'significantly increases our acquaintance with human pyramidal cells, laying the foundation for constructing models for other (excitatory and inhibitory) neuron types in the human brain, and paving the way for constructing models of human cortical microcircuits and exploring its dynamical repertoire in silico, as has been recently performed for rodents cortical microcircuits'.

The pyramidal neuron is a multipolar neuron found in the hippocampus, the amygdala, and the cerebral cortex – the well-known folded structure that envelopes the brain and is implicated in cognitive ability.

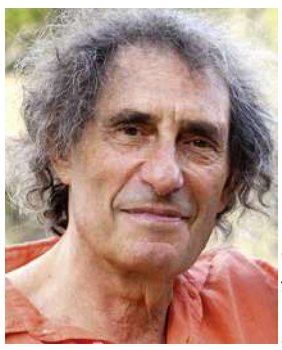
Human brain tissue is difficult to acquire for research, so neuroscientists generally use animal tissue for their work.

Through this research they have learned a lot about how mammalian brains work but have not been able to clearly decipher what makes us uniquely human, in, for example, our advanced cognitive abilities.

When comparing rodent and human brains, it is the cerebral cortex that is so obviously more developed in humans. The human neocortex (part of the cerebral cortex) has many thousands more nerve cells, is substantially thicker with more synaptic connections per cell, and the pyramidal neurons are larger.

The lead author of the paper, Professor Idan Segev, from the Department of Neurobiology in the

**Continued on page 2**



Source: Idan Segev

**Professor Idan Segev works at the Department of Neurobiology at the Hebrew University of Jerusalem, Israel**

www.healthcare-in-europe.com

## Discovered: what make us humans

Continued from page 1

Hebrew University of Jerusalem, Israel, said that, to really understand the human brain and what makes us human, 'it is essential to study the human brain at the detailed level of cells and the synaptic connections'.

He explained that this can be challenging because of the complexity of the human brain and because of ethical and technical limitations.

'To overcome these limitations, we built 3-D computer models of human neocortical pyramidal cells. We chose cortical pyramidal neurons because they are the most abundant cell in the cortex,' he explained. 'Ramon y Cajal, the researcher who discovered pyramidal neurons, called them "the psychic cell".'

'The pyramidal neurons are larger in humans than in rodents and they also have more dendritic branches, which potentially makes them a more sophisticated computing device. As such, "what makes us human" also implies that, even at the single-cell level, we are more computationally-sophisticated,' Segev observed.

Their detailed digital model for human cortical pyramidal neurons is the first to integrate these distinct anatomical and physiological features, thus enabling the team to identify several new properties of human neurons and analyse their functional implications using advanced computational tools. Pointing to the difficulties of this research, he said it was a challenge to obtain the neuronal tissue from the hospital, recording and reconstructing the neurons and then making sure that the computer model was accurate. The team used a cluster of computers to ensure the model fitted their experimental requirements as well as to speed up the computations. They also developed new algorithms to help this fit.

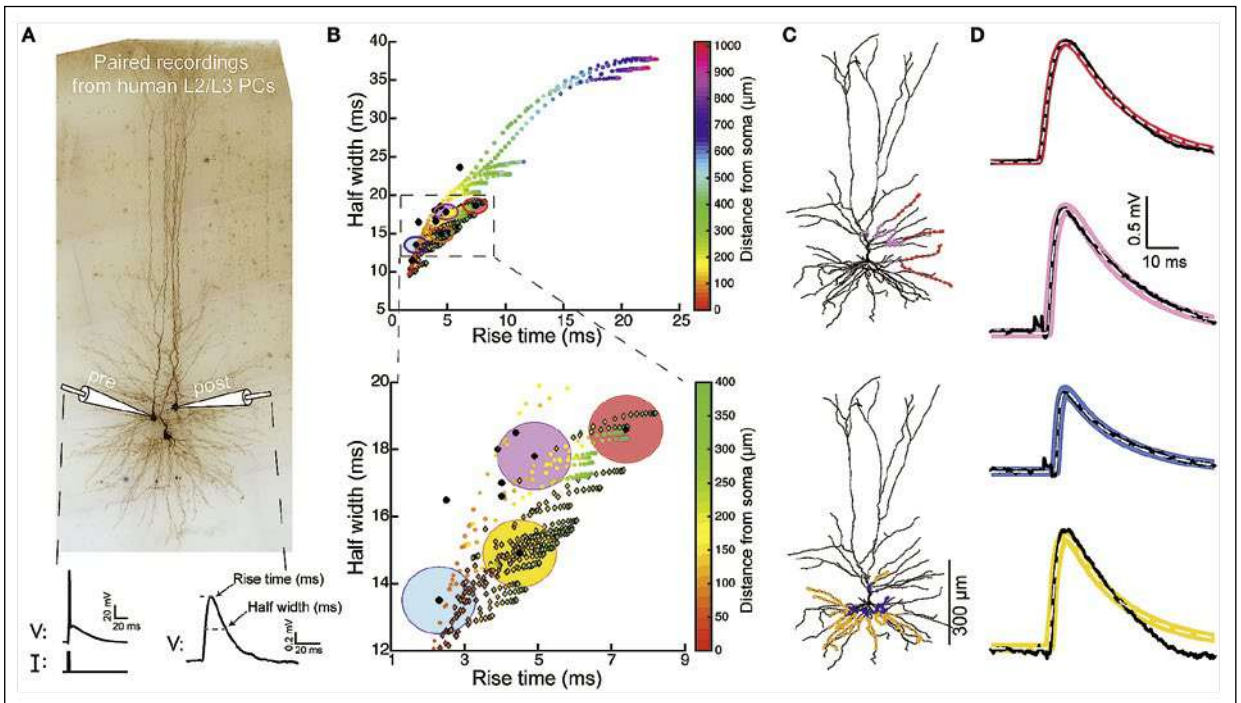
Their computer models revealed how human pyramidal neurons efficiently process a larger number of more powerful synaptic inputs, assisted by their lower membrane capacitance, compared to rodents' neurons. 'Human cortical cells have unique membrane properties, with more efficacious excitatory synapses that compensate for their highly-branched and elongated dendritic tree.

'Combined, these properties boost their computational power,' Segev explained. 'This suggests that human neurons, compared to rodents' neurons, are fundamentally more powerful in their ability to integrate, process and store information. These cells support nearly double the number of simultaneous, independent synaptic inputs to be conveyed from the dendrite to the cell body, which explains the enhanced computational capability of these cells. Unlike biopsy material, their computer model can integrate plastic processes at the synaptic level – thus the neuron model and its synapses may change due to the cell's activity in the computer model. 'We were quite surprised by our findings,' he added. 'We weren't aware of the enhanced complexity of human neurons compared to rodents.'

Segev, looking at what lies ahead with this research, said: 'We have made significant advances modelling human hippocampal neurons – the "memory region" of the brain.

'In the next decade we will see a growing effort, worldwide, to understand the human brain at the local circuit level. Next, we want to build a whole human cortical circuit – like we did for the mouse under the "Blue Brain Project".'

Sources: Frontiers in Cellular Neuroscience:; Blue Brain Project:; Frontiers Science News.




**Model predicts that HL2/L3–HL2/L3 excitatory synapses are formed at proximal dendritic sites. (A) Pair recording from HL2/L3 PCs. A presynaptic spike was initiated in a cell (lower left trace) and the postsynaptic EPSP was measured in another cell (lower right trace). The shape index of this EPSP is defined by its rise time and half-width (bottom right). (B) Top: Theoretical shape-index curve for the modelled cell shown in (C), as a function of distance from the soma. Colours code for the physical distance from the soma; colour circles for apical inputs and colour diamonds for basal inputs. Bottom: Zoom-in into the square demarcated at the top frame. Black circles are from 10 experimental somatic EPSPs. The large filled colour circles with radius of one ms are centred around the loci of the respective four experimental EPSPs shown in (D). (C) Modelled cell used in (B), with dots depicting the predicted synaptic locations that give rise to somatic EPSPs whose shape indices fall within the corresponding large coloured circles in (B). For example, red points are all synaptic contacts that yield rise-time and half-width that are within the red circle in (B). (D) Four experimental EPSPs (black traces) from four connected pairs of HL2/L3-HL2/L3 pyramidal cells and the theoretical EPSPs (100 model fits, per experimental EPSP, in colour traces, with their mean depicted by the dashed white line) corresponding to the respective colour dots in (C). The peak synaptic conductance, for each of the putative dendritic synapses, was obtained by fitting the theoretical to the experimental transients. The recordings in (A) were taken from a pair of cells that were not reconstructed, and the HL2/L3 morphologies are shown here only for illustration of the method.**

*Early preparation pays off, but hurdles remain*

# Software gains highest-risk MDR certification

**Medtech companies** operating in Europe are preparing for a busy year, with the end of the transition period for the European Union's Medical Device Regulation (MDR) fast approaching. After the May 2020 deadline, all new medical devices must meet MDR requirements in order to be placed on the European market. Meanwhile, existing devices that have already been certified under previous legislation will have to be recertified under the MDR by 2024.

In September, Berlin-based Biotronik achieved the industry's first MDR certification for a device in the highest-risk Class III category, after obtaining approval for its Renamic Programmer software. The company says the achievement comes down to a preparation effort dating back three years, but that challenges still remain to meeting MDR requirements in time.

The MDR replaced both the previous Medical Device Directive and the Active Implantable Medical Device Directive with a single regulation governing product certification across the EU. Although companies have until 2024 to recertify existing products, parts of the MDR remain open to wide interpretation, says Roman Borkowski, Biotronik's Senior Vice President, Quality Management and Regulatory Affairs, Cardiac Rhythm Management. This leaves open the question of how firms might have to adapt while the regulatory ambiguities are gradually clarified over the next few years.

**Biotronik Renamic Programmer. The Renamic's software was the first Class III (highest-risk) product worldwide to achieve certification under the new MDR.**

'The "MDR journey" has only just begun and there's still a long way to go,' he says and points out that while Biotronik agreed on a transition plan with its notified bodies earlier this year to recertify existing products, the firm anticipates it will have to use almost the full length of the transition period for legacy products that ends in 2024. 'Although manufacturers are preparing themselves as best as possible, complete guidance has not yet been published, many standards have not been harmonised, the majority of necessary implementation acts have not been adopted, and common specifications do not exist yet.'

With the number of products that must be recertified, in addition to the new technologies companies will seek to launch on the European market, Borkowski predicts regulatory bodies may be heavily backlogged – especially towards the end of the transition period.

So, what can organisations do? Some are expected to pull certain existing products rather than recertify them. on this, Borkowski recommends that companies do whatever they can do to prepare now with the information currently available.

'The faster a manufacturer starts with the practical implementation of the known interpretations of the MDR, the easier it will be to adapt later and ultimately implement the necessary changes successfully in order to comply with the MDR,' Borkowski points out. Biotronik began with a cross-department project in 2016 to first recertify its programmer software. The firm also focused on collaborating with numerous industry association working groups across Europe, to gain a sense of how the MDR was likely to work in practice. This helped to prioritise products, like the Renamic Programmer software, that are widely used but required less expert panel involvement to achieve certification.

Borkowski argues it is a harder result to duplicate in other products, 'but we are prepared to fulfil the conditions required for recertification until 2024,' he points out. 'Many changes to legacy products will be limited during this time because any such changes, for example ones involving component availability, would require immediate certification under the MDR. But we are confident that the steps we're taking will allow us to ensure a seamless continuity of supply during a challenging time for how we handle regulatory compliance.'

**Roman Borkowski, Senior Vice-President for Quality Management and Regulatory Affairs, Cardiac Rhythm Management at Biotronik**

*Implant healing, less complicated*

# ‘Smart’ coatings protect endoprosthesis

**Physicists from the University of Augsburg, together with colleagues from Hamburg and Munich, have developed a material that is particularly toxic when bacteria are present in its environment. In the future, this „smart“ coating could help prevent complications in the healing of endoprostheses. The coating also offers further advantages: It is extremely wear-resistant and yet at the same time so rough that bone cells adhere well to it.**

**Today, the implantation** of artificial hip or knee joints is part of everyday surgical practice. One problem that doctors have to contend with is infections near the prosthesis. They delay healing and can impair the stability of the connection between the endoprosthesis and the bone. ‘The situation is further complicated by the fact that more and more bacteria are becoming resistant to common antibiotics,’ explains Dr Christoph Westerhausen from the Department of Experimental Physics I at the University of Augsburg. ‘This forces us to look for alternatives.’

One such alternative could be the innovative coating that the research team has now developed and tested. This is a wafer-thin coating made of diamond-like carbon, which experts call ‘DLC’. DLC coatings are extremely resistant. But the key feature of the new coating lies elsewhere: ‘We dope it specifically with zinc oxide particles,’ emphasises Westerhausen. ‘Zinc ions are toxic to microorganisms; the dissolution of zinc oxide is also strongly dependent on the pH value of the solution.’ Unfortunately, though, the heavy metal has a significant disadvantage: it can also damage or even kill body cells. However, as long as the zinc oxide is embedded in the DLC layer, there is no danger. Only when the nanoparticles dissolve in the tissue fluid and the zinc thus becomes a freely mobile ion does it unfold its toxic potential.

## When the wound becomes acidic

Infections are often accompanied by a reduction in the pH value. The scientists‘ idea was that perhaps this would lead to the carbon coating releasing its zinc content, primarily in the presence of bacteria. ‘That was why we initially produced tiny zinc oxide particles,’ explains the biophysicist. ‘Each of them was not even one twentieth as thick as a bacterium.’ Then the researchers stirred this ‘heavy metal dust’ into a liquid polymer solution and used it to wet their test implants. They then converted the thin polymer film into DLC using a sophisticated process.

They tested the resulting coating for its behaviour at different pH values. Normally, the tissue fluid is neutral to minimally alkaline; in case of inflammation, however, it becomes slightly acidic. In fact, the zinc oxide dissolved much faster under these conditions. The coating released about thirty percent more zinc ions in the initial phase of the release when the pH was lowered by one level. In microbial tests, the researchers were also able to show that the coating can effectively inhibit the growth of bacteria – especially at an acid pH value. Among the microbes tested were also those that are resistant to various antibiotics and that therefore frequently cause problems after operations.

Admittedly, tissue cells were also damaged by the zinc ions. ‘However, the effect also occurs with an acid pH,’ stresses Dr Westerhausen. ‘In such a situation, however, the advantage far outweighs the disadvantage. In further tests, the scientists want to vary different parameters of the new coating to further optimise the effect.

**EUROPEAN HOSPITAL**

**ERRATUM**

**EUROPEAN HOSPITAL issue 5/2019**

**Please accept our apology for the following error on page 14: The article ‘A focus on sports imaging’ published in this issue contains incorrect information and should not have been published.**

**The article in question was published without approval of the doctor interviewed for this article.**

*TAITRA at Medica 2019*

# A vision of Taiwan innovation

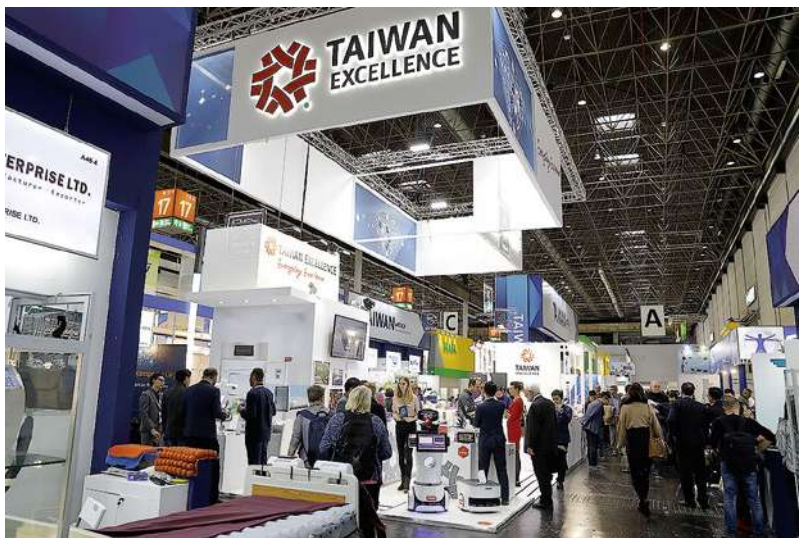
**A popular proverb in Mandarin goes 'Hearing something a hundred times is not as good as seeing it once' (百聞不如一見). Visiting the Taiwan pavilion at this year's Medica, it's clear to see that the Bureau of Foreign Trade (MOEA) from Taiwan, together with the Taiwan External Trade Development Council (TAITRA) and its foster companies, have taken this sentiment to heart. Seeing virtual and augmented realities through a VR headset, watching AI in digital pathology through the eyepiece of a microscope – the power of images was clearly on the exhibitors' side. They showed their guests some of the innovations that have propelled Taiwan from former manufacturer nation to one of the leading developers in medical technology and healthcare solutions.**

Report: Wolfgang Behrends

**'We are looking at** a new wave of Taiwan innovations to transform the medical world', announced Karen Pai during the 'Taiwan Excellence' press conference. As Deputy Executive Director she underlined the ambitious expansion of med-tech TAITRA promotes as 'Best Made in Taiwan' with its impressive growth rate of 10.73 percent in 2018. It is hard to deny the nation's global impact. 253 Taiwanese companies presented their products at Medica 2019. Every year, 20 of this country's manufacturers are awarded the 'Taiwan Excellence' accolade to acknowledge their outstanding approaches to VR/AR, 5G, AI and robotics in medical applications.

At Medica, manufacturer HTC DeepQ presented the latest refinement of their virtual reality set, the Vive Pro Eye, as well as a 5G hub. Whilst both products may be geared towards entertainment, their use in healthcare is also apparent.

With new eye-tracking features, the Vive Pro Eye analyses the wearer's attention and focus areas. 'This creates a whole new level of immersion, for example in augmented reality surgery training', explained Lewis Chang, Product Development Manager at HTC DeepQ. At this point Richard Vincent, CEO of FundamentalVR joined the conversation. The company's software – a 'flight simulator for surgeons', as Vincent put it – now supports the advanced features of the Vive Pro Eye. This is complemented by the HTC 5G hub, which provides the high-speed mobile data infrastructure for advanced wireless medical equipment, VR and telemedicine.




**Five winners received the coveted Taiwan Excellence award**


**The potential of VR for surgery was explored by HTC subsidiary DeepQ**

Virtual realities are also the domain of Taiwan Main Orthopaedic Biotechnology, another 'Taiwan excellence' winner. The firm's CEO, Min-Liang Wang PhD, brought improved versions of the company's smart surgical glasses and virtual anatomy table. The new editions expand the application areas from medical education and intricate procedures like spinal surgery to minimally-invasive techniques. A new 3-D endoscopy system, coupled with smart glasses, provides detailed insight into a patient's body via augmented reality, with critical anatomical structures and instrument position superimposed on the viewer's glasses. 'The additional information shortens procedure duration, improves the overall outcome and puts less strain on the surgeon', Wang PhD explained.

## Counting on AI counting

Artificial intelligence in medicine is a definitive mainstay at Medica, so the great enthusiasm for aetherAI's digital pathology solution was hardly surprising. Their AI model, named Hema, specialises in the automatic differential cell counting of a bone marrow smear – a vital task to discern specific forms of leukaemia. 'Five years ago, this was an impossible challenge for imaging solutions', aetherAI CEO and co-founder Joe Yeh. 'With the help of AI, we now can.' Trained with a dataset of 300,000 annotated bone marrow cells, the Hema AI can perform in five seconds what might otherwise take up to half an hour – even for a well-trained haematologist.


**aetherAI presented a cell counting algorithm for leukaemia differentiation**

**Visitors were keen to connect with the 'Taiwan Excellence' winners during Medica 2019**

**Robots might soon guide patients and families through hospital visits – some Taiwanese hospitals have already begun to deploy these mechanised helpers**

The spread of knowledge is the driving force behind the wireless medical camera developed by Taiwanese manufacturer Faspro. This head-mounted device can record up to 24 hours of video footage and enables live streaming. This is more than just a GoPro for doctors, company representative Adam Horng stressed. 'Instead of providing a wide "fish-eye" perspective, our camera features a narrow field-of-view – 10 to 28 degrees – and autofocus with low minimum distance, to accommodate for surgery and dentistry settings.' Other than sharing videos for educational purposes, the system is designed to reduce the burden of procedure documentation. Accessories for the camera system include an advanced light source and foot pedals for hands-free recording control.

An advanced video streaming solution was presented at Medica by Advantech. Based on the company's expertise as a provider of integrated computing systems, the system, named AVAS, manages video inputs from multiple 4K sources. This allows for combination and simultaneous display of up to four different camera feeds, vital monitors, radiology images, virtual 3-D patient models and more, while integration into the hospital information system (HIS) ensures compatibility of many different formats.

## Strengthening relations

In addition to the five 'Taiwan Excellence' winners highlighted at the Taiwan Excellence press conference, the Taiwanese pavilion at Medica presented an impressive range of novel and improved healthcare products, from robotic clinical assistants and rehabilitation helpers to point-of-care and monitoring solutions. 'The relationship between Taiwan and Germany is growing stronger', concluded Juan Carmona-Schneider, senior consultant for healthcare at the European enterprise networking organisation ZENIT. With the continued support of their respective governments and increasing number of innovative products, it is just a matter of time until Taiwanese healthcare solutions gain a strong foothold in European hospitals and doctor's practices.

# Liquid biopsy offers advances for cancer diagnosis

**Liquid biopsy offers a new dimension to detection and stratification of cancer – yet the technique also faces hurdles and challenges in becoming a mainstream diagnostic approach that will help facilitate more personalised treatments.**

**Report: Mark Nicholls**

**A critical challenge** lies in identifying the extremely low concentrations of the bio-analytes of CTC (circulating tumour cells), ctDNA (circulating tumour DNA) and exosomes in the blood, explained Professor Klaus Pantel, Director of the Institute of Tumour Biology at the Hamburg Eppendorf University Medical Centre in Germany.

He believes, however, that this is an evolving technique which will offer benefits to patients and healthcare systems in terms of better diagnosis, targeted treatments and cost effectiveness. The professor outlined the 'current clinical application and challenges' at a recent conference held in Corfu, which looked at liquid biopsy advances.

Speaking to European Hospital after the meeting, he said a prime clinical application of liquid biopsy is in screening and early diagnosis of cancer 'with the goal to find small tumours early enough to cure them by surgery'. However, he added: ' We have to develop and use extremely sensitive methods because, to detect small tumours, we need to detect very small amounts of circulating DNA or circulating tumour cells or EVs (extracellular vesicles).'

He explained how good sensitivity and specificity are needed to detect tumour types but the approach can require a combination of different biomarkers (e.g., circulating DNA and proteins) to achieve high accuracy.

Source: Shutterstock/Mega Pixel

A second application of liquid biopsy can be to assess individual risk in cancer patients. 'This can be done with circulating tumour cells and new data with circulating DNA that helps to subdivide patients into different risk categories beyond usual TNM staging,' he said.

'We can also use blood sampling to follow up patients during the post-surgical period and see whether we see any early molecular relapse detected in the blood, before the imaging tells us there is metastases.'

Pantel said the process can be honed to determine the therapy offered to patients – both those who are not fully metastatic and already have adjuvant or neo-adjuvant therapy, or those with full-blown metastases that can be seen from imaging analysis.

Ultrasensitive assays that enable the reliable detection of minute numbers of circulating tumour cells, or amounts of ctDNA, should be implemented into clinical trials of neoadjuvant and/or adjuvant therapies, he added, and might also complement imaging procedures currently used for post-surgical surveillance of tumour relapse.

CTCs or ctDNA can also help identify potential druggable alterations on the DNA or druggable pathways.

Examples for druggable genetic alterations are the mutations in the EGFR gene in lung cancer and for druggable alterations that are the variant expression of androgen receptor in prostate cancer. 'These are very good examples of using liquid biopsy analysis to better say which individual therapy works in individual patients,' Pantel explained.

However, he said the major challenge remains in the fact that the bio-analytes of CTC and ctDNA are in such low concentrations in the blood. 'The tumour is only a small part of the total body and the signal that comes from the tumour is also just a small signal in the blood so that is really the challenge,' he continued.

With smaller tumours, the challenge is to subtract the signal from the noise. Additionally, in older patients, there are mutations that do not necessarily lead to cancer, so there is background noise too.

He stressed the importance of testing the robustness and reproducibility of these methods, in particular with low DNA concentration from the tumour. Such work is currently being undertaken by the European Liquid Biopsy Society (ELBS) and other bodies.

Latest innovations include developing methods with in-built controls, while in the CTC field advances are in measuring tumour cells in vivo.

Wearables, he suggested, will play a role with the advent of devices that, within the next five years, will continuously measure and collect CTCs, addressing the problem of low concentration. While this lies in the future, there are already clear benefits from liquid biopsy for patients and healthcare systems.

'If we can better stratify patients in terms of individual need for an expensive cancer therapy, we will save money because we will not waste expensive therapies on the wrong patients,' Pantel added. 'Using this technology to better define which patients may profit from it has a benefit both for the patient and the healthcare system.'

He concludes that liquid biopsies of blood samples for quantitative and qualitative assessments of CTCs and ctDNA can provide new insights into the disease stages in cancer patients and lead to more targeted treatments.

**Klaus Pantel** is Professor of Medicine at the University Medical Centre Hamburg Eppendorf, Hamburg, in Germany and Director of the Institute of Tumour Biology as well as a member of the executive board of the university's comprehensive cancer centre. He is also Coordinator and Director of the European Liquid Biopsy Society.

*AI plus blood test could revolutionise care*

# Early brain tumour detection – within minutes

**A simple blood test coupled with artificial intelligence (AI) analysis could help spot the signs of a brain tumour sooner in patients.**

**Report: Mark Nicholls**

Brain tumour diagnosis is difficult: patients often see their family doctor (GP) several times before referral for a scan. However, research presented at the 2019 National Cancer Research Institute (NCRI) Cancer Conference in Glasgow last November suggests the blood test – combined with machine learning – could detect a brain tumour within minutes.

The University of Edinburgh and University of Strathclyde researchers hope the non-invasive test will simplify and speed up diagnosis; provide an efficient, accurate and cost-effective option to identify brain tumours, and deliver better stratification of those needing urgent brain scans.

Lead researcher Dr Paul Brennan explained that, following the blood test, which generates complete data sets for patients, Attenuated Total Reflection Fourier-transform infrared (ATR-FTIR) spectroscopy is used to identify the cancerous biosignature in serum and differentiate between glioblastoma and primary cerebral lymphoma. An AI pattern recognition algorithm then shows which samples indicate brain tumour.

'Spectroscopy gives a snapshot of thousands of molecules at once,' he explained, 'but we wouldn't be able to analyse that data without a machine learning approach. While not knowing which the important molecules are that predict the difference in behaviour, we do know that we can reproducibly identify them in the tumour population and identify their absence in the non-tumour population. So, the real innovation is to be able to handle large amounts of data and not have to pre-suppose a biological mechanism. That's where the opportunity is.'

Brennan, a senior clinical lecturer and honorary consultant neurosurgeon at the University of Edinburgh, acknowledged there remain delays in diagnosing brain tumours because symptoms are often non-specific, with no methods currently in place for early detection of brain cancer. Consequently, 62% of patients are diagnosed in emergency departments. 'A headache,' he added, 'could be a sign of a brain tumour, but it's more likely to be something else and it's not practical to send many people for a brain scan, just in case. The challenge is identifying who to prioritise for an urgent scan.'

The researchers say the simple blood test at this early stage could facilitate stratification of patients to be prioritised for urgent brain imaging.

In a previous study, 765 blood serum samples were collected from patients diagnosed with various types of brain cancer, with three robust machine learning techniques – random forest, partial least squares-discriminant analysis and support vector machine – yielding promising results.

From blood samples from 400 patients with possible signs of brain tumour and referred for a brain scan at the Western General Hospital in Edinburgh, and patients with a recent brain tumour diagnosis, the test correctly identified 82% of brain tumours and 84% of people with no brain tumour, meaning it had a low rate of false positives. With glioma, the most common form of brain tumour, the test was 92% accurate at picking up tumours. Funded by Scottish Enterprise, the experimental study 'Prospective clinical validation of novel serum biomarker test for the identification of patients at risk of brain tumour' concluded: 'This rapid screening test could revolutionise triage of patients in primary care suspected of having a brain tumour, helping to prioritise the most at-risk for rapid imaging.'

Emphasising the breakthrough would not be possible without AI, Brennan stressed this was not a case of AI speeding up a human process, but a new process that would be unavailable without AI.

'What we now have is a test that doesn't cost very much, gives rapid results, and those who get a positive result go and get their CT scan,' he said.

The blood test will not replace the brain scan, which will remain a critical component for neurosurgeons to assess tumour position and type, but it could help reduce the number of patients being scanned, with earlier identification of patients potentially leading to better outcomes. 'We are future-proofing and also providing a platform technology because the technique has the potential to be adapted to other difficult to diagnose cancers,' Brennan added. A next step is to use the test on 600 more patients referred for a brain scan and then work with regulators, the NHS and the primary care sector towards making it available in the UK.

Brennan worked with Dr Matthew Baker from the University of Strathclyde to develop the test. Baker said: 'These results are extremely promising because they suggest that our technique can accurately spot who is most likely to have a brain tumour and who probably does not. This could ultimately speed up diagnosis, reduce the anxiety of waiting for tests and get patients treated as quickly as possible.'

**Paul Brennan** is Senior Clinical Lecturer and Honorary Consultant Neurosurgeon at the University of Edinburgh and NHS Lothian. He combines his surgical work with laboratory research into the origin of gliomas and is also active in clinical research.

*Screening for the use of 5-FU anti-cancer drug*

# Fully-automated DPD deficiency testing

**Each year almost 80,000 new patients in France alone receive fluoropyrimidines, a group of anti-cancer drugs including 5-FU which is normally administered intravenously to treat digestive, breast and head and neck cancer.**

Interview: Daniela Zimmermann

**However,** fluoropyrimidines-based chemotherapies can cause severe toxicities (incidence at around 20%) and sometimes lethal toxicity (incidence between 0.1 and 1%) with part of these toxicities possibly related to deficiency in the activity of the main enzyme enabling elimination of 5-FU, dihydropyrimidine dehydrogenase deficiency (DPD).

Because of this risk, routine screening for DPD deficiency before treatment with fluoropyrimidine is now necessary.

EH asked Stéphane Moreau, who is responsible for LC/MS in Europe for the Japanese instruments and medical equipment manufacturer Shimadzu Corporation, to outline what is available for this kind of screening and any new developments.

Two methods currently exists to diagnose DPD deficiency, he said, but underlined that each involves a significant amount of manual work. One is genotyping, though key to that is in knowing the different variants to detect. 'It's not 100 percent accurate,' Moreau observed, 'because you detect only what you know.'

The second technology is LC-MS/MS, which has the advantage that the ratio of uracil and Dihydrouracil is measured directly. 'As uracil is metabolised to $UH_2$ by DPD, the ratio $UH_2$/U reflects the DPD activity, thus indicating a risk for the use of 5-FU drugs. In this way, you can identify the DPD deficiency, even if you don't know the different genes influencing the DPD deficiency.

'In genotyping,' Moreau added, 'you are looking for the genes that are the cause of the deficiency while, with LC-MS/MS, you estimate the activity of DPD by measuring the ratio of compounds $UH_2$ and uracil. In one case you look at the cause, in the other, you look at the result.

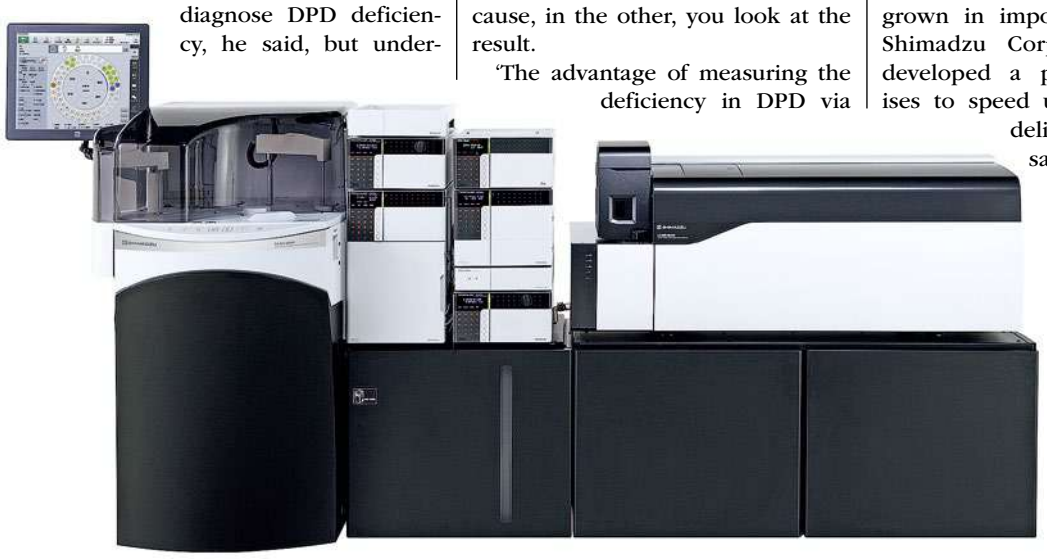
'The advantage of measuring the deficiency in DPD via the ratio U/$UH_2$ is that you will take care of all deficiency cases, thus eliminating the risk of toxicity. In that way, this is safer.'

However, he did acknowledge that the problem with LC-MS/MS is that sample preparation is 'quite tedious, with a lot of manual steps' and has been limiting penetration of LC-MS/MS.

## The fully-automated LC-MS/MS method

Potentially leading to toxicity and bone loss by reduction of 5-FU metabolism, DPD has a big impact on the use of the cancer drug 5-FU (5-fluorouracil). Thus DPD identification is key to identifying those patients who may be susceptible to a negative reaction to 5-FU and help to avoid that serious reaction.

Additionally, with the ever-increasing number of tests needed, automating this process has grown in importance. Fortunately, Shimadzu Corporation has now developed a process that promises to speed up testing and also deliver greater accuracy, safety and standardisation. The answer has been to develop a fully-automated LC-MS/MS method for uracil and dihydrouracil in human plasma, known as indirect phenotyping.



Previous LC-MS/MS methods encountered problems with complex liquid/liquid or solid-phase extraction procedures. However, Moreau explained that Shimadzu has developed a method in which the extraction is carried out by a programable liquid handler directly coupled to a liquid chromatograph (LC) MS/MS system.

Specifically, the extraction procedure is performed by a CLAM-2030 coupled with a LCMS-8060 triple quadrupole mass spectrometer.

Now, with the increasing number of tests required – and the new French guidelines introduced in December 2018 that state that all patients treated by 5-FU should be checked for DPD enzyme deficiency – coping with demand and throughput is a challenge, due mainly to the long sample prep process.

Due to the complexity of liquid extraction and the manual steps, Shimadzu received a request from a customer using its CLAM robot to develop a method to automate the preparation process prior to LC-MS/MS. 'That completely automated this,' Moreau said, 'and reduced the analysis time with a solution for the customer to increase the throughput in their lab.'

## France has now installed its first systems

Recently validated at a hospital in Limoges, the first systems in France are being installed. Moreau believes this will attract widespread interest in other countries. He points to a presentation, last June at the European Association of Pharmacology and Toxicology in Sweden, from scientists in Leiden regarding their systematic genotyping process with a profile for each patient, but also showing that, with this, there are still cases of toxicity because they do not know all the variants that cause this problem.

'So, I'm sure LC-MS/MS is the best solution and that automated sample prep will help a lot of people.' The automated process is time-saving, improves workflow and offers standardisation. The Shimadzu LC-MS/MS approach has cut manual sample prep time from 30 to 10 minutes or less, but a major benefit is that the next sample is being prepared while the existing sample is being run on the system, increasing throughput. Sample analysis is also reduced to 15 minutes.

After the sample is placed on the robot there is no need for human manipulation and, as the robot handles every sample in exactly the same way, standardisation is high.

With so many cancer patients receiving 5-FU-based chemotherapy, Moreau stressed that the importance of finding out quickly about DPD deficiency is now widely recognised and he believes the Shimadzu solution of automating sample prep and a LC-MS/MS method to measure uracil and dihydrouracil with no human intervention once the sample tube is positioned, is set to play a key role in speeding up this process, and offer better and quicker outcomes for patients.

In 1994 **Stéphane Moreau** obtained his diploma from INSA in fine chemistry and engineering with a specialisation in chemical process engineering. He then began his professional career in laboratory equipment distribution before joining the brand new Shimadzu France subsidiary in 2002. Since then, he has held various positions to develop the MS range business. Since September 2013, he is product manager for the MS range with Shimadzu Europe.

*Critical lack of skilled lab workers*

# Addressing the lab technician shortage

**The UK and Europe are facing a serious lab skills shortage over the next decade with medical laboratories among the worst affected, Mark Nicholls reports.**

**An ageing population** and skilled operators retiring without being replaced by a new generation of lab technicians is at the core of a critical lack of skilled lab workers, with it taking 5-10 years for a technician to become fully competent and an expert in their field.

The current challenges facing the technical community were outlined at the Lab Innovations 2019 conference Birmingham, UK, by National Technical Development Centre (NTDC) Director Natalie Kennerley, who pointed to the lack of recognition, career pathways and training as major issues to overcome in ensuring 'a sustainable technical workforce for the future'.

'The skills shortage within the UK and Europe is very serious,' she said. 'Not only are laboratory skills in short supply, but also increasing numbers of creative arts-based skills are also vulnerable. We have an ageing population who have an extensive knowledge formed over many years within their roles, which will be lost if we cannot find ways to address this problem.'

Research carried out by the Gatsby Foundation has indicated that, by 2030, the UK will require a further 700,000 technicians to support the economy. Kennerley suggested that today's graduates are often not 'work-ready' in terms of understanding how hands-on practical processes work and lack the practical experience to do the job and solve the problems that technical staff work on every day. 'In the UK, technical roles status is not where it should be. By contrast, in Germany the technician is a highly regarded and respected individual.'

All areas of research could suffer but, she pointed out that this could be particularly acute in the medical arena. 'If we cannot recruit the right people to do the job, then those areas are at serious risk of collapse,' Kennerley added. 'Histology technicians working with hospitals and research institutions are key to ensuring that valuable experimental and/or patient tissue samples are tested/treated correctly and the results produced are accurate and meaningful. Learning to fine tune methods and techniques is a skill built up over many years and cannot simply be learned quickly from textbooks but requires hands-on practical experience.'


The NTDC has developed tools to enable organisations to address these issues, with close links to the Technician Commitment initiative launched in the UK in 2017 to raise the profile of technical staff.

With work required to promote technical careers to the next generation of technicians, steps being taken by the NTDC and other bodies to avert the crisis include promotion of secondments, work shadowing opportunities, apprenticeships and working with schools and colleges to promote careers within the technical community.

The NTDC also provides bespoke tools to support organisations in ensuring they have an engaged, motivated and skilled workforce which is future fit. These include the technician Roles, Responsibilities and Skills audit; the Higher Education Career Pathway tool; the technician development framework. The NTDC has also launched a new online portal designed to capture continuing professional development, and has gathered data to identify high risk areas and help to influence national policy.

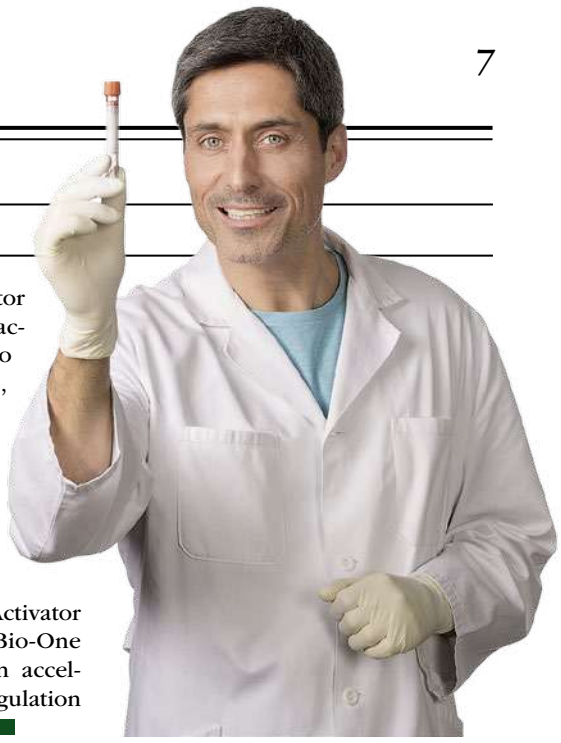
'Training and development of technical staff is also fundamental to the delivery of new and cutting-edge technologies and organisations need to be encouraged to find resources to support staff training and development,' Kennerley added. This approach can also lead to a much more engaged and motivated sector as they see the value their organisation places on them and their willingness to invest in their development.'

While Artificial Intelligence (AI) also has a role to play in areas such as auto analysers and robotic samplers, she stressed that additional appropriate training is essential to optimise AI advances.

'Employers will try to introduce this technology as a way of efficiency savings (staff costs reduction) but will need to realise specialist highly trained and skilled technicians will still be needed (and at a

*Serum analysis fast as plasma analysis*

# 40 minutes test rate down



**When test results** are needed very quickly 'Greiner Bio-One's Vacuette Cat Serum Fast Tube is the first on the market to combine the quality of serum analysis with the speed of plasma analysis,' the manufacturer Greiner reports. Serum can be analysed as quickly as plasma. Coagulation takes just five minutes.'

## Fast coagulation increases quality and efficiency

'The quality of a laboratory is frequently measured by how many samples can be processed within a given time. The indicator is the turnaround time (TAT), i.e. the time between an analysis being ordered and receipt of the result. That time is radically reduced by using the Vacuette Cat Serum Fast Tube. Thanks to the short coagulation time – just five minutes, followed by centrifugation for 5–10 minutes, the analysis of key clinical chemical parameters can begin after only 10–15 minutes, allowing reliable results to be attained far quicker. That is a major time-saving compared to the usual duration of 40 minutes when using conventional serum tubes.

'The added gel forms a stable barrier between the serum and cellular components of the whole blood after centrifugation. The sample quality is better preserved thanks to the short coagulation time, Greiner Bio-One adds. 'Coagulation takes just five minutes, which virtually rules out post clotting in the laboratory. As a result, preanalytical errors are reduced and accurate values can be used for diagnosis.'

## Serum vs. plasma

'Owing to the fast turnaround time, plasma tubes continue to be used for many analyses. However, determination of certain parameters on the basis of plasma is not appropriate for some tests,' explains Thomas Ehrenfellner, Product Manager for Vacuette tubes at Greiner Bio-One GmbH in Kremsmünster. In some cases, incorrect values may result from the presence of anticoagulants or fibrinogen in the plasma tube. The use of serum is therefore indispensable in many cases.

## For doctor's surgeries

The tube is also valuable for use in doctor's surgeries. 'Analyses performed on site can be evaluated more quickly, reducing waiting times for both the doctor and patient,' the manufacturer continues. 'Thanks to the short coagulation time, blood collection is also possible shortly before transport to the laboratory.'

## Special coating

The tube is coated with a mixture of Blood Clotting Activator (BCA) and thrombin,' Bio-One explains. 'Thrombin, as an accelerator, speeds up the coagulation process.'

**Natalie Kennerley** is Director of the National Technician Development Centre, which provides other organisations and their technical communities with access to information, expertise and research and tools designed to support the delivery of high-quality technical services across all areas, including creative arts, media, medical and science.

more advanced level) – programming the equipment and analysing the data output.'

However, Kennerley concluded, 'Despite the challenges to the sector, there has never been a better time to be a technician. With the support of organisations such as the NTDC and the Science Council and with the help of initiatives such as the Technician Commitment we will make a difference – the future is bright.'

*Therapeutic proteins at peak among pharmaceuticals*

# Sports drug testing gains powerful aids

**Due to the scientific and technical developments in recombinant DNA technology and protein engineering since the early 1980s, therapeutic proteins have emerged as one of the most important classes of new pharmaceuticals. Currently, more than 200 protein and peptide based drugs have gained approval by the USA's Food and Drug Administration (FDA) and many more are under preclinical or clinical investigation.**

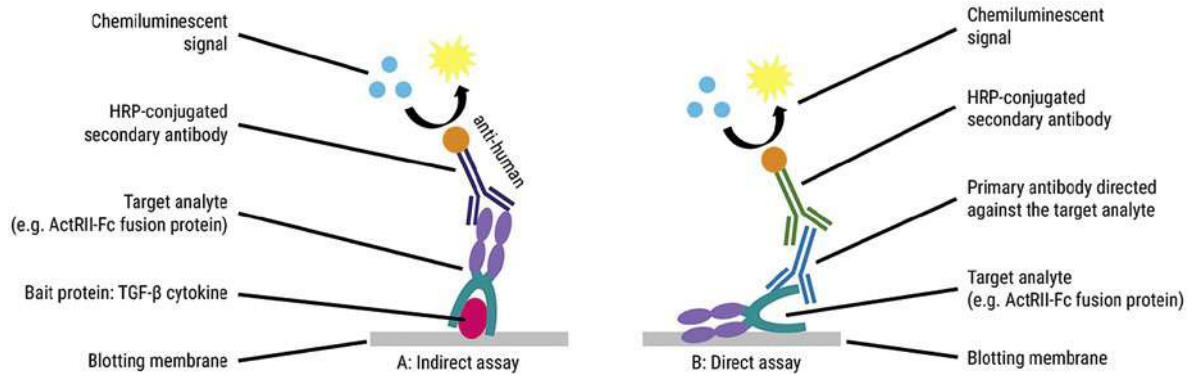
Report: Katja Walpurgis & Mario Thevis

**These comprise recombinant** versions of natural proteins (e.g. growth factors, enzymes, anticoagulants) as well as engineered proteins, protein conjugates, Fc fusion proteins, and recombinant therapeutic antibodies. Both protein re-design and chemical modifications such as glycosylation and PEGylation are strategies that can be employed to extend the serum half-life and improve the effector functions of a protein drug. Moreover, the construction of Fc fusion proteins through the attachment of an immunoglobulin G1 (IgG1) Fc domain to a protein or peptide can provide IgG-like properties, such as a long serum half-life, due to recycling through the neonatal Fc receptor (FcRn) and a slower renal clearance. Therapeutic antibodies are comparably stable molecules, which bind their targets with high affinity and specificity. Therefore, they constitute the largest and fastest growing class of protein drugs. At present, more than 50 chimeric (approx. 70% human sequences), humanised (85-90% human sequences), and fully human antibodies are approved for the treatment of autoimmune diseases, cancer, and other disorders.

Both the approved and investigational protein/peptide therapeutics comprise several drug candidates with potential performance-enhancing properties, whose misuse in sports is restricted under the terms of the World Anti-Doping Code (WADC). While protein drugs such as erythropoietin and its derivatives, human growth hormone (hGH), and human chorionic gonadotropin (hCG) can be detected by using immunological approaches such as Western blotting and luminescent immunoassays (LIAs), liquid chromatography and high-resolution mass spectrometry (LC-HRMS) are routinely used to test doping control samples for the presence of peptidic compounds such as insulins and growth hormone releasing peptides (GHRPs).

The proactive development of specific and sensitive detection methods for emerging protein/peptide therapeutics still missing clinical approval is the main task of preventive doping research. Many of the protein-based drugs currently undergoing clinical investigation have the same therapeutic target: TGF-β cytokines such as myostatin, activin A, and GDF-11.

While myostatin is considered as the key negative regulator of skeletal muscle mass, both GDF-11 and activin A were found to inhibit late-stage erythropoiesis. Additionally, activin A is involved in the regulation of bone formation and recent studies suggest that the cytokine could also play a role in muscle growth inhibition. TGF-β cytokines exert their bio-




**Indirect vs. direct Western blats for the detection of therapeutic proteins in sports drug testing. In indirect assays (A), a protein drug is detected on the basis of its properties (e. g. affinity for a TGF-ß cytokine and presence of a human Fc domain. In direct assays (B), the compound is bound by a highly specific primary antibody, which can subsequently be detected by a species-directed secondary antibody.**

**Dr Katja Walpurgis** studied Biology at the University of Bonn. Since gaining her PhD in 2013, she works as a postdoctoral researcher at the Centre for Preventive Doping Research/Institute of Biochemistry of the German Sport University Cologne. Her work focuses on the development of novel detection methods for performance-enhancing protein drugs by using different proteomics techniques, such as gel electrophoresis, western blotting, and high resolution accurate mass LC-MS.

**Dr Mario Thevis** graduated in organic chemistry and sports sciences in 1998. He gained his PhD in Biochemistry in 2001 and did post-doctoral research at the Department of Chemistry and Biochemistry at the University of California Los Angeles (UCLA) in 2002. After being a senior researcher (2003-2005) he became Professor for Preventive Doping Research at the German Sport University Cologne in 2006. In August 2017, he accepted the position of Director of the Institute of Biochemistry of the German Sport University in Cologne.

*The Heraeus Symposium at DKOU*

# The challenge of Periprosthetic infection

Report: Beate Wagner

**Periprosthetic joint infection** (PJI) is on the increase internationally. In Germany, for example, around 14,500 cases of PJI in hip and knee replacements occur annually. 5,100 of those are caused by multidrug resistant pathogens. 'Eighty-seven percent of those affected die within five years,' orthopaedic surgeon Professor Rudolf Ascherl MD pointed out during the Heraeus Symposium held at the German Congress of Orthopaedics and Traumatology (DKOU) held in Berlin, this October.

Life expectancy is lower than for those affected by prostate cancer, breast cancer and melanoma, and quality of life is severely impaired. 'The condition has chronic, almost oncological characteristics and patients suffer both physically and mentally for years,' he added. 'Twelve in 100 patients even state that they would rather die. We need a better understanding of who the high-risk patients actually are to get a better handle on PJI', Ascherl believes.

According to British studies, overweight, multimorbid patients with heart, kidney or liver problems, and often further implants along with knee or hip endoprostheses, are at particular risk.

'The present classification of PJI into acute or chronic stages does not sufficiently reflect the complex individual situation,' according to Professor Volker Alt, from the Clinic and Polyclinic for Trauma Surgery at Regensburg University Hospital.

A new classification of PJI developed by Volker Alt and team now offers the prospect of improvement. This is to provide a clearer indication if a patient is still suitable for an intervention, from which type of intervention they could benefit and if, like many of those affected, they have already undergone one or several revisions. 'Like other classification systems, PJI classification must consider all key factors, such as implant, pathogen and morbidities. The condition of the soft tissue, concomitant diseases and whether or not the patient can be anaesthetised are also important.

'The new classification may sound complicated,' Alt observed, 'but it's basically designed to clarify everything that needs to be addressed in a structured manner, before any kind of treatment. 'In future, all treatment options are to be based on this,' Ascherl said.

PJI is one of the main reasons for around 72,000 revisions of hip and knee joint replacements. These often complex interventions carry a risk of their own.

Amputation is not uncommon. 'If patients wear unsuitable spacers for too long, for instance, or if foreign bodies are not completely removed, we should talk about the option of amputation,' Ascherl explained. He recommends this in cases where sepsis and three relapses have already occurred. In each case, weighing up exarticulation and amputation must be on an individual basis.

According to experts, the challenge of PJI can only be met in a multidisciplinary, professional setting – with a consistently standardised treatment algorithm, for instance – as implemented at the Centre for Musculoskeletal Surgery (CMSC) at the Charité University Hospital in Berlin. 'Our multidisciplinary concept factors in specifics such as nosocomial pathogens, the condition of the bones and soft tissue, as well as the stability of the endoprosthesis,' said Professor Andrej Trampuz, Specialist in Infectious Diseases and Head of the Department of Septic Surgery at the Charité Berlin. The standardised procedure has reduced the occurrence of relapses from 10.4% to 3.1%. 'However, the increasing use of local antibiotics, implant coating and bacteriophages is new.'

Trampuz emphasised the importance of treating PJI as early as possible. 'If the implant is to be preserved, the infection must not be older than a maximum of four weeks,' the infection specialist advised. During this acute phase, sufficient surgical debridement, the administration of systemic and local antibiotics and, if applicable, the exchange of the mobile prosthetic components, have priority.

Once this early phase has passed, the persistent biofilms can no longer be eradicated even with biofilm-active antibiotics. 'The objective is always the least invasive treatment option, with the best functional result without negative impact on the cure rate,' Trampuz explained. 'The importance of preserving the implant has increased considerably over recent years.'

After four weeks, PJI is regarded as chronic. There are around 6,500 of these late-stage infections every year, 4,000 in hip replacements and 2,500 in knee replacements. At this stage, those affected have now most definitely become high-risk patients. 'If nosocomial pathogens are involved, when bones and soft tissue are in bad condition, and where the endoprosthesis is unstable, the only options are complete revision or lifelong suppression,' said Trampuz.

The objective is always a one-stage exchange with a short interval. A Berlin study confirms the advantages. 'Combined with local and systemic antibiotics this demonstrably reduces recurrences,' he added. 'During this late phase it's important that the antibiotics are biofilm-active. Examples of this are rifampicin, ciprofloxacin, penicillin and fosfomycin.

The combination of several antibiotics in the bone cement is advocated to prevent resistance. The different active agents attack the bacterial metabolism in different

**The experts gathered at the Heraeus Medical Satellite Symposium. From left: Professors Andrej Trampuz, Rudolf Ascherl, Klaus-Dieter Kühn and Volker Alt**

logical functions through binding to activin type II transmembrane receptors (ActRIIs).

Consequently, agents specifically blocking the receptor-ligand-interaction are considered as promising therapeutics for the treatment of various diseases, including muscle wasting disorders and anaemia.

For cheating athletes, these drugs represent promising alternatives to classical doping agents such as anabolic steroids and erythropoietin, which can potentially be misused to illegally increase muscle mass and red blood cell count.

Current strategies for myostatin inhibition comprise drug candidates specifically targeting the cytokine such as anti-myostatin antibodies, peptibodies, and adnectins, follistatin-Fc fusion proteins, and agents derived from the myostatin propeptide, as well as multi-targeting approaches as, for example, anti-ActRII antibodies and ActRII-Fc fusion proteins acting as receptor competitors. Such decoy receptors were also developed to stimulate red blood cell production through neutralisation of circulating GDF-11 and activin A.

As some of these unapproved compounds are already available for research purposes and distributed on the black market, specific and sensitive detection methods were proactively developed, either in collaboration with the pharmaceutical industry or by using reference proteins intended for research purposes for method development and characterisation.

In order to detect the myostatin-neutralising antibody Domagrozumab and the anti-ActRII antibody Bimagrumab in doping control serum samples, affinity purification employing magnetic beads coupled to GDF-11 and ActRIIB-Fc was used, in combination with SDS-PAGE and Western blotting or tryptic digestion and LC-HRMS. While the Western blot-based assay indirectly demonstrates the presence of a myostatin-binding protein with a human Fc-domain (figure A), the LC-HRMS methods specifically identify Domagrozumab and Bimagrumab at the amino acid level. Both the LC-HRMS assays and Western blotting approach have detection limits in the lower nanogram per millilitre range (Bimagrumab: 20 ng/mL; Domagrozumab: 50 ng/mL; sample volume: 200 µL).

## Clinical study with Bimagrumab

The analysis of authentic post-administration samples obtained from a clinical study with Bimagrumab demonstrated that such a sensitivity is sufficient to detect these drugs for at least several weeks following injection.

A broad range of doping control detection methods was also developed to identify the erythropoiesis-stimulating Fc fusion proteins Sotatercept (ActRIIA-Fc) and Luspatercept (modified ActRIIB-Fc) from plasma, serum, and dried blood spots. For the isolation of the target analyte(s) from the biological matrix, magnetic beads coated with the TGF-β-cytokine activin A, the bacterial IgG-binding protein Protein G, or specific antibodies directed against the extracellular receptor domain were employed. The resulting sample extracts were subsequently analysed by using Western blotting or LC-HRMS: An electrophoretic separation by means of SAR/SDS-PAGE or isoelectric focusing (IEF) was combined with Western blotting in order to identify the separated intact molecules with antibodies directed against the extracellular receptor domains (figure B).

By contrast, the MS-based detection methods are highly specific for proteolytic signature peptides of the fusion proteins. The detection limits of the assays developed for plasma and serum varied between 0.1 and 50 ng/mL (sample volumes: 50-1000 µL). In dried blood spots, Sotatercept could be detected at concentrations as low as 250 ng/mL (sample volume: 20 µL). Again, this should enable detection windows of at least several weeks, as both Sotatercept and Luspatercept have to be administered at high doses of several hundred micrograms per kilogram bodyweight.

Most of these approaches can easily be modified to include further protein drugs as soon as authentic reference material is accessible. Moreover, they serve as proof-of-concept for the detectability of emerging TGF-β inhibitors and expand the range of available tests for protein therapeutics with performance-enhancing properties.

places. 'My standard recommendation is the combination of clindamycin and gentamicin or a high dose of gentamicin plus vancomycin in the bone cement as they are locally effective, antibacterial and biofilm-active,' Trampuz advised.

For primary joint replacements and aseptic revisions Trampuz recommends the prophylactic administration of 0.5-2g of antibiotic per 40g of cement; for septic revisions 2-4g per 40g cement. 'Local, highly dosed administration prevents colonisation of spacers and supports the eradication of infection,' he pointed out.

The combination of different antibiotics also produces important effects of synergy, as Professor Klaus-Dieter Kühn, from the Medical University of Graz reported. 'Clindamycin for instance, is antibacterial in high concentrations, extremely able to permeate the bones and thus helps other antibiotics to move from cement into bone. There is also strong synergy between vancomycin and gentamicin. This combination has proved itself in the fight against multidrug resistant pathogens.'

Highly dosed, locally administered combinations of antibiotics are also suitable for infection prophylaxis. A British study involving 848 patients after bipolar hemiarthroplasty for displaced intracapsular femoral neck fracture showed that those who had been prophylactically given 1g each of gentamicin and clindamycin (Copal G+C) had a 66% significantly lower risk of infection than those with standard antibiotic loaded bone cement (0.5g gentamicin, Palacos R+G). Alt uses this protocol as standard at Regensburg University Hospital.

*The future of endovascular interventions*

# Robotic angioplasty

**An exciting development from an innovative French company is poised for a major breakthrough in European markets, Jane MacDougall reports.**

As is now well-known, coronary angioplasty is a procedure that widens and/or unblocks the arteries to the heart by the insertion and inflation of a balloon and/or stent into the vessel lumen. In modern practice, a stent is normally left in place to ensure the blood flow remains unhindered. Known collectively as percutaneous coronary intervention, PCI, angioplasty with stenting is one of the most widely performed procedures worldwide.

Driven by the burden of cardiovascular disease on human health, the specialty of PCI is characterised by continuous growth and rapid advances in technology in the quest for better results. While innovations in stents, guidewires, catheters, suturing and of course imaging have facilitated outcomes over many years, it is only relatively recently that robotic assistance for PCI has been considered with the CorPath robotic system from Corindus (USA) being the most advanced to date.

## Close collaboration with interventional cardiologists

A French company, Robocath, based in Rouen, was set up in 2009 by Dr Philippe Bencteux to design, develop and commercialise robotic systems to help treat cardiovascular diseases. Robocath, which now has more than 25 employees, has received financial support from regional and national investment funds. Its business model involves close collaboration with European interventional cardiologists to achieve a robotic system fit for purpose. By so doing, their robotic platform, R-One, has become the first European robotic solution to obtain the CE mark for use in interventional cardiology.

Professors Durand and Sabatier using the robot at Rouen University Hospital


Preparing the R-One for an intervention

Dr Fajadet, from the Clinique Pasteur in Toulouse, at the R-One control panel

Obtained in February 2019, the CE mark means that the system can now be commercialised in Europe and the Middle East. Dr Bencteux explains that the potential for the system in Europe alone is enormous, with the possibility to install it in more than 3,000 procedure rooms and perform around 1.6 million interventions annually.

The company is currently working to finalise a number of strategic distribution partnerships in geographic areas with high potential. The R-One is expected to launch throughout Europe and the Middle East in 2020.

Thanks to the practical approach to its design, R-One integrates seamlessly into cath lab protocols without introducing additional steps. The robot, which suits femoral or radial access, provides reliable and precise assistance to enhance the cardiologist's movements for a better clinical outcome. The possibility of remote delivery and manipulation of guidewires and stent/balloon devices during PCI has the added advantage of protecting the operator from radiation exposure. Clearly, ionising radiation is a constant in the work life of cath lab teams, potentially subjecting them to long-term health issues.

R-One consists of two core elements, a radio-protected control station from which, protected by a mobile radiation screen, the physician can remotely control the instruments by joysticks, and the robot with its articulated support arm. The robot is compatible with all leading manufacturers' devices: guidewires, stents, balloons and imaging systems, and is very easy to install.

Although the learning curve is minimal, operators should first obtain specific training from Robocath on the use of the system before attempting to perform any intervention. Training sessions are provided on a frequent basis.

## First two coronary angioplasties with R-One

This September, the first two coronary angioplasties were performed with assistance of the R-One robotic platform. These successful procedures were undertaken at the Rouen University Hospital by Professors Durand and Sabatier, and at the Clinique Pasteur in Toulouse by Doctor Fajadet. The participating teams are very encouraged by these initial results and highly positive about the outcomes from the forthcoming trial they are also involved in. The safety and efficacy of the R-One platform in coronary angioplasty will be investigated in a prospective clinical trial. The first of its kind in Europe, the study will enrol 60 patients from six different centres, three of which are based in France (Rouen University Hospital, Caen University Hospital, Clinique Pasteur in Toulouse) and the other three in the Benelux countries.

Judging by Siemens' planned acquisition of Corindus for a purchase price of US$1.1 billion at the end of this year, robotic assistance is now very much recognised as the future of endovascular interventions. Robocath intends to be part of this. Among its R&D efforts, the group is exploring the possibility of robotic assistance in stroke and other vascular emergencies to guarantee all cardio-vascular patients benefit from the best care pathway available.

**Dr Philippe Bencteux** is president and founder of Robocath. He has an MD from Caen University and specialist qualifications in radiology, medical imaging and business strategy. He also works as a radiologist in a private clinic in Rouen while maintaining his active involvement in the evolution and development of the R-One platform.

*Hospital in Wesel is a Senhance Reference Centre*

# A new era in minimally invasive robotic surgery

**Report: Sonja Buske**

**The Protestant Hospital Wesel** (EVK Wesel) is one of two reference centres in Germany and one of 25 worldwide for the Senhance® Surgical Robotic System from Transenterix. 'We wanted to be the first in the Lower Rhine region to go to market with a robotic system as we believe that this type of digital surgical assistance represents the future,' explains Rainer Rabsahl, CEO of the 356-bed hospital.

'We have been a very innovative healthcare institution ever since our foundation,' says Rabsahl. The EVK Wesel was one of the first hospitals in the Lower Rhine region to set up an Oncology Department, a Stroke Centre and a Nephrology Department. The EVK Wesel is also amongst the pioneers in hip and knee endoprosthetics. 'For a hospital of our size and especially in a rural region, this is not a matter of course. Luckily, we have always had a good feel for which innovations are likely to become established,' explains the CEO.

The Senhance Surgical Robotic System for minimally invasive procedures in general and visceral surgery was introduced in Wesel at the beginning of August. It provides the surgeon, who sits next to the patient in a comfortable position at an open console during the operation, with pin sharp, high resolution images enlarged up to six times. The camera is controlled with the surgeon's eye movements, the instruments inside the patient's abdomen are controlled via the hands. An integrated tremor filter eliminates the slight jitters experienced by everyone. This facilitates working with a level of precision not otherwise possible with human hands.

It is this precision which has already attracted a lot of attention and is very sought after. 'We have patients who come to us and explicitly state that they want this device to be used for their surgery,' reports Rabsahl. 'We have not seen any fear of, or scepticism towards robotically assisted surgery.' 40 operations were carried out between August and October, with a target of 240 per year. Says Rabsahl: 'However, I must emphasise that we will not operate on patients who do not require surgery. We do not carry out more operations just because we have a new system. The patient obviously always comes first.'

The advantages for the patient are obvious though: Surgery is less invasive due to smaller incisions and therefore smaller scars, with less wound pain. The system in Wesel is used for hernia operations, gall bladder removal and oncological, abdominal interventions. Cancer patients benefit particularly from the new technology. It is planned to extend the use of the system to gynaecological interventions as well. 'We are taking this step by step, as stipulated in the training plan for surgeons,' explains Rabsahl. 'Training with the new robot takes a certain amount of time, and at the moment each intervention is supervised by an external doctor experienced in using the robotic system. We can also draw on constant support from a Transenterix technician. Safety is our main priority."

Rabsahl reports that his staff are proud to work in a hospital which can afford such modern equipment. 'This investment was certainly a financial challenge for our hospital, but we look at this as a means of safeguarding the future.'

The hospital specifically aims to attract the attention of young doctors in this way and hopes that the robotics system will provide a competitive advantage which will also have an impact on economic viability in the long run.

The EVK Wesel is not only a reference centre but also an observation and practice centre: interested surgeons and students can gain an insight into surgical procedures of the new generation – and may become motivated to return as employees at a later stage.

**Rainer Rabsahl** is CEO of EVK Wesel GmbH since 2004. The qualified business economist is also responsible for several health centres and care facilities that are predominantly located on the large campus area.

*Significant improvement in cleaning, disinfection and sterilisation*

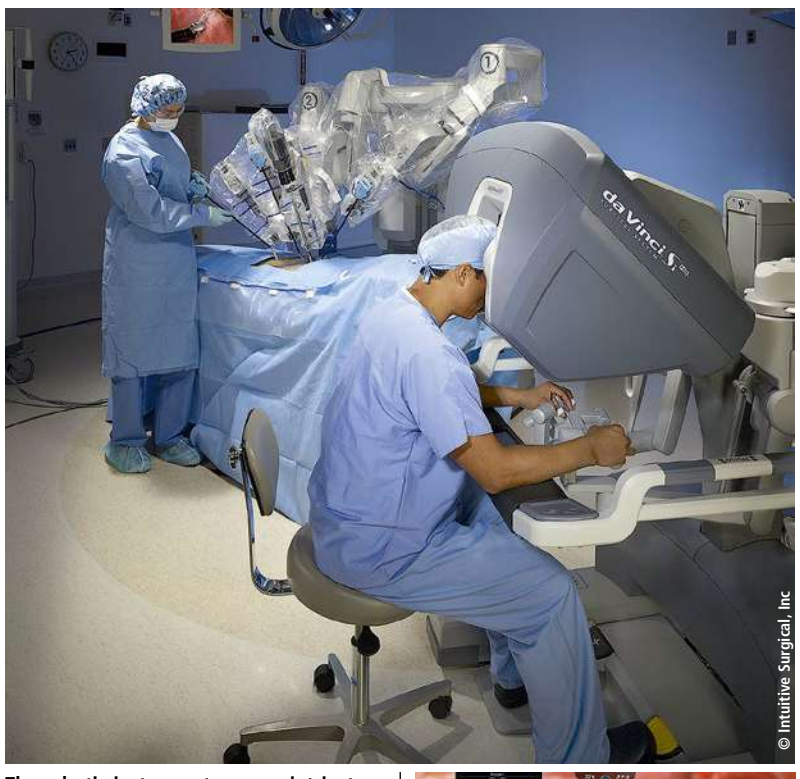
# Surgical robots must also be hygienic

**Modern healthcare without hand hygiene? Inconceivable – particularly in the operating room (OR). But what happens when it is not the surgeon who handles the scalpel, but a robot? Robotic surgery, just like surgery performed by humans, always carries a risk of microbial transmission to the patient, says Professor Johannes K-M Knobloch of University Hospital Hamburg-Eppendorf (UKE). A specialist in microbiology, virology and infection epidemiology and Head of Hospital Hygiene in his institution, Knobloch explains how robotic systems are cleaned, disinfected and sterilised to prevent infections.**

Report: Wolfgang Behrends

**Several surgical robots** work at UKE in Hamburg, where the Da Vinci systems are mainly used for prostatectomies and for intra-abdominal surgery. 'The robotic arms themselves are hardly subject to contamination,' microbiologist/virologist Knobloch explains, 'since the systems have a smooth surface and were designed to be cleaned easily.' For most minimally invasive procedures the surgical robots are equipped with click-on devices that are removed after surgery and cleaned, disinfected and sterilised separately.

**Professor Johannes Karl-Mark Knobloch** is a specialist in microbiology, virology and infection epidemiology and head of the hospital hygiene department at the University Medical Center Hamburg-Eppendorf (UKE). His research focuses on the development of microbial biofilms, for example on implants. He is a member of the German Society for Hygiene and Microbiology (DGHM) and the German Society for Hospital Hygiene (DGKH).

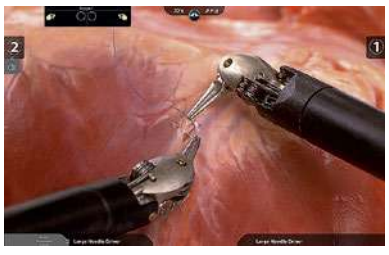



**The robotic instruments use an intricate array of small Bowden pulleys for operation and positioning**

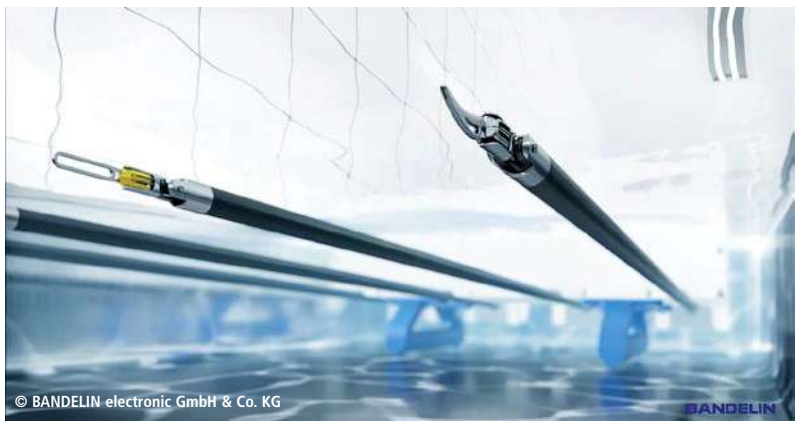
## Smaller and more complex

The array of instruments available to the surgical robot corresponds largely to what is available to human surgeons – often in miniaturised form and with some adjustments. The robot, for example, does not cut with a sharp knife but burns tissues with electro-cauterisation.

The robotic instruments often contain tiny mechanical components. In surgery, graspers, clamps or needle



holders with a complex Bowden pulley mechanism are used. This construction, which is necessary for the robot to be able to position the instruments more precisely in the body, comes with a drawback, Knobloch finds: 'Cleaning and disinfecting is much more complicated than with a conventional one-piece scalpel.'




From the hygiene aspect, the thin wires that open and close, tilt and angle the instruments present a challenge. 'During interventions, these wires move back and forth many times. With each pull they also pull contaminated material, such as tissue, blood and protein from a patient's body,' the hygiene expert explains; indeed 'in the early days of robotic surgery, it was a real problem to remove all protein particles from the robot parts and prepare them for the next patient.'

## From the OR right to the cleaners

With technology progressing, cleaning, disinfection and sterilisation also improved significantly. To avoid protein drying and caking on the instrument, the parts are submerged in a cleansing solution immediately after an intervention. Special ultrasound baths remove most of the particles. In a final step the instruments are treated in a thermal washer-disinfector. Modern surgical robots feature specific connectors which allow thorough cleansing. 'This sophisticated multi-step procedure can only be performed by specially trained staff. You need to handle these robotic instruments on a daily basis and get to know them; otherwise your cleaning might result in errors,' Knobloch says. Therefore, at UKE robot parts are cleaned, disinfected and sterilised separately from conventional OR instruments.

Additionally, manufacturers of surgical robots provide guidance about cleaning and disinfection of their products. The recommendations are to a large extent the result of learning processes by clinicians and manufacturers alike, says Knobloch: 'User feedback has contributed a lot to the development of cleaning best practices. The manufacturers use clinicians' feedback, integrate it and pass new recommendations back to the surgeons who provide feedback again. Over the past few years, this feedback loop has led to sophisticated cleaning/disinfection documentation.'

## A worthwhile effort

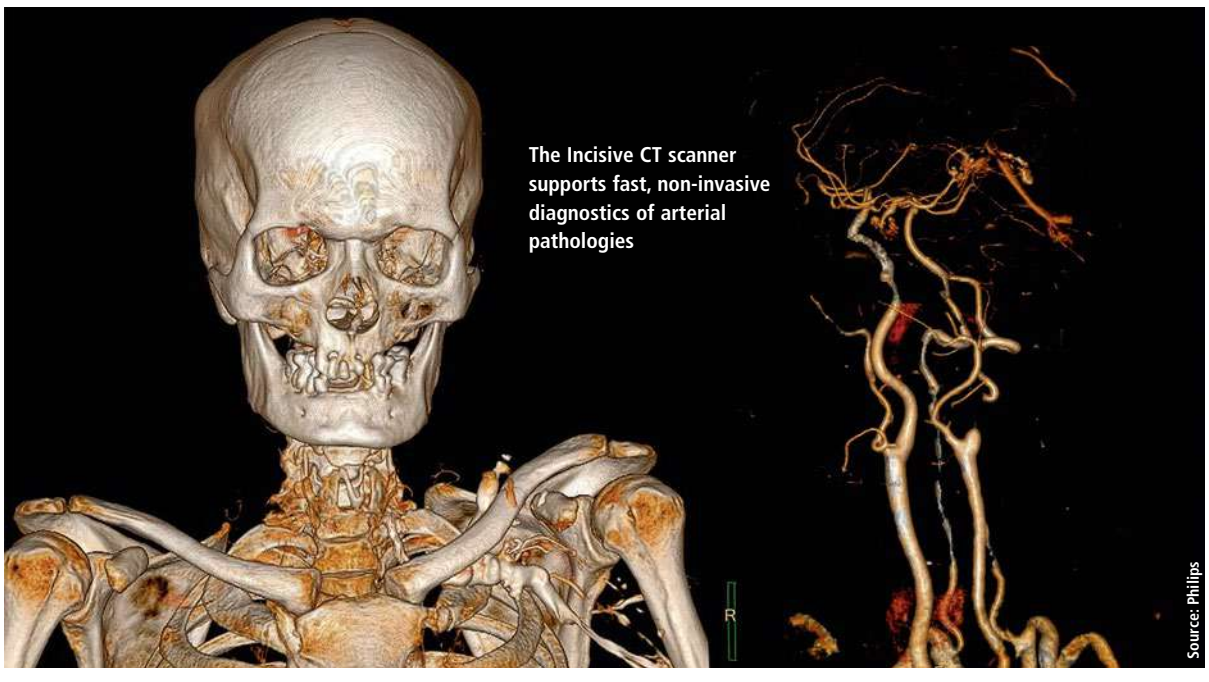
Due to their complex architecture, the cleaning and disinfection procedure for robotic instruments is much more time-consuming than that of conventional surgical instruments. 'The effort, however, is worthwhile.' Knobloch believes, 'since experienced operators of surgical robots achieve better patient outcomes. The smaller incisions performed by the robots translate into less bleeding and fewer infections. Furthermore, patients can be mobilised faster because their abdominal muscles remain intact.'

The expert's summary is positive: Surgical technology and post-surgical treatment might be more expensive and more time-consuming than conventional approaches, but the benefits clearly outweigh these disadvantages.

*Reference institution thoroughly tests CT system and potential*

# New Incisive CT is 'outstanding'

**A new CT scanner created by Philips and installed in Berlin's Zehlendorf district in October, is Germany's first Incisive CT. The machine is now demonstrating its outstanding capabilities of modern computed tomography at the Diagnostic Department of Theodor-Wenzel-Werk e. V. (TWW), a reference institution which is part of a network operated by the Protestant Church.**



The Incisive CT scanner supports fast, non-invasive diagnostics of arterial pathologies

Source: Philips

**TWW includes a clinic,** three in-patient care facilities, two assisted living facilities and an out-patient department. It is also among the top institutions for mental health. 'We have expert teams that treat medical conditions that continue to stigmatise patients, their families and even the care staff. We are proud that we were able to strengthen our profile with innovative medical technology, particularly in radiology,' says Managing Director Bernd Jakobs.

In addition to psychiatry and psychotherapy, the TWW clinics offer psychosomatic-psychotherapy care with a focus on internal medicine and neurology. Being a fast and robust procedure, computed tomography is used primarily for head, spine and vessels exams.

## Efficient, intuitive and close to the patient

'The Incisive CT provides an intuitive workflow with a self-explanatory user interface that requires little training. OnPlan patient-side gantry controls allow the radiographer to work right at the scanner – which saves time and movement. However, more importantly, the radiographer is also right next to the patient which is a major quality feature above all in the care of vulnerable patient groups. Not only cooperation-impaired patients benefit from reduced exam times. A study by the Oz Radiology Group has indicated that the system can potentially reduce scan times by almost 20 percent,' Philips points out. 'The shorter the time in the gantry, the less likely are spontaneous movements and thus the need for sedation or repeat scans.'

## High image quality, low dose

Modern medical technology aims at reducing the physical and mental patient stress connected with a CT scan. This entails protecting the patient from the harmful effects of ionised radiation. Incisive CT features DoseWise Portal, a web-based dose monitoring solution that collects, measures, analyses and reports radiation exposure in line with applicable law, and helps to optimise dose, while maintaining high image quality.

Since artefacts impair diagnostic conclusivity, iDose4, an iterative reconstruction technology, ensures noise-free images with high spatial resolution even at low dose.

In view of demographic changes, more and more patients with endoprostheses will need to be scanned. Incisive CT is equipped with O-MAR, a technology that reduces artefacts caused by large orthopaedic implants.

At TWW's neurological department, many patients suffer from spinal pathologies. Here, O-MAR is helpful in follow-up imaging after stabilisation surgery. Moreover, the 70 kV scanning protocol enhances contrast resolution at low dose. With this system, radiology at TWW 'made major progress,' says Bernd Jakobs and adds that 'the system achieves significantly better image quality in shorter scan times and with lower radiation exposure, which means we can offer our patients a faster and more precise diagnostic work-up.'

## Future-oriented platform: designed to grow alongside needs

Being a scalable platform, the Incisive CT flexibly adapts to the user's specific needs and requirements. To provide the entire range, from routine applications to highly complex cardiac and Dual Energy scans, TWW's Diagnostic Department is equipped with the full system. Interested radiologists and radiology technicians have the opportunity to familiarise themselves with the new scanner in regular operating mode. TWW is looking forward to the benefits of the new system.' As a reference institution,' adds Jakobs, 'we could thoroughly test the systems and the potential it holds for patients and users before a final investment decision was taken.'

Another benefit: TWW will become an attractive cooperation partner for office-based radiologists who can use the new system to offer their patients a broader array of CT exams than with their current equipment.

**Bernd Jakobs, Managing Director of TWW E.V.**


Source: Philips

**OnPlan patient-side gantry controls on both sides of the gantry allow the user to stay close to the patient**



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

**Editor-in-Chief**: Brenda Marsh

**Editorial team:**
Wolfgang Behrends, Sonja Buske

**Senior Writer:** John Brosky

**Executive Director:**
Daniela Zimmermann

**Founded by** Heinz-Jürgen Witzke

ISSN 0942-9085

**Correspondents**

**Austria:** Michael Krassnitzer, Christian Pruszinsky.

**China:** Nat Whitney

**France:** Jane MacDougall

**Germany:** Anja Behringer, Annette Bus, Walter Depner, Cornelia Wels-Maug, Holger Zorn

**Great Britain:** Brenda Marsh, Mark Nicholls.

**Malta:** Moira Mizzi

**Spain:** Mélisande Rouger, Eduardo de la Sota

**The Netherlands:** Madeleine van de Wouw.

**USA:** Cynthia E. Keen, i.t. Communications, Lisa Chamoff

**Subscriptions**

Dorothea Fleischer, Theodor-Althoff-Str. 45, 45133 Essen, Germany

**Subscription rate**

6 issues: 42 Euro, Single copy: 7 Euro.

Send order and cheque to:

European Hospital Subscription Dept

**Printed by:** WVD, Möhrfelden, Germany

**Publication frequency:** bi-monthly

**Representatives**

**China & Hongkong:** Gavin Hua, Sun China Media Co, Ltd.
Phone: +86-0755-81 324 036
E-Mail: 627416876@qq.com

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

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

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

**Israel:** Hannah Wizer, International Media Dep. of El-Ron Adv. & PR Co., Ltd.,
Phone: +972-3-6 955 367
E-Mail: ronin@netvision.net.il

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

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

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

*AI assists at molecular level*

# Expanding human vision

**Physicians have long trusted in the human eye's ability to perceive differences on a microscopic or even radiological level. One of the most important areas for artificial intelligence (AI) will be to expand human vision not just in radio-diagnostics, but also histology and microscopic diagnostic imaging, according to Dr Andrés Cervantes, President-elect of the European Society for Medical Oncology (ESMO).**

**Report: Mélisande Rouger**

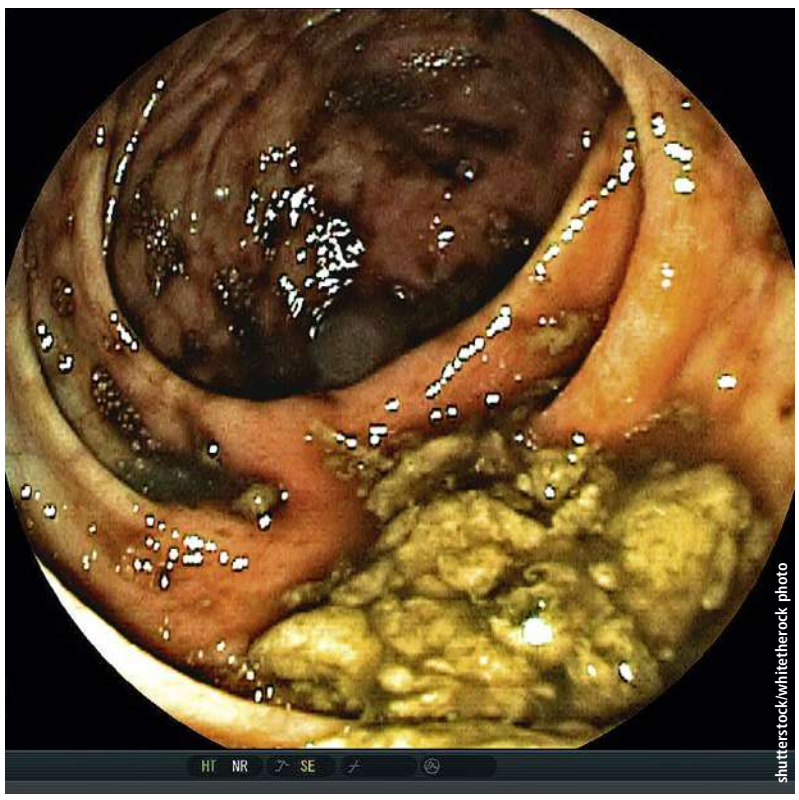
**AI models will** enable microscopic image analysis in greater detail and with greater accuracy. 'One of the most recent deep learning convolutional neural networks performed better than experienced dermatologists at detecting skin cancer.

The development of AI tools means that doctors will no longer need to try and decipher images by themselves. Much faster, more efficient and more readily available systems will help them do so,' said Cervantes.

An image, however, is not just something to look at. It is also a source of information that can be mined. With the growing role of big data in medicine, much more precise and accurate systems of analysis can be generated. Huge amounts of data can be extracted for future patient management – and that includes molecular data.

Radiomics helps collect information on textures, patterns, the amount of liquid in a tissue, how much blood it receives, etc. But a lot of knowledge can also be taken from molecular analysis. Genetic studies generate a large quantity of information, which requires dedicated analysis and interpretation to improve diagnosis.

'There is information of which we are probably not making enough use. I think that at diagnostic level, we'll have imaging, microscopic pathology and clinical radiomics. We will have molecular diagnosis,' he said, 'and not just for mutated genes, but also to detect genes that will have variants or alterations related to the action of, or resistance to, medicine. A series of barriers are being broken in this sense.'




**Upper Gastrointestinal Endoscopy: The Legacy Project is focused on stomach cancer.**

## Promoting research beyond Europe

As scientific director of INCLIVA, one of Spain's accredited research institutes, Cervantes is involved in various international studies, one of which will enable to share knowledge between Europe and Latin America.

The Legacy project is part of the Horizon 2020 EU program and will receive funding of around €4m over a three-year period. It will allow the transfer of European technology and pedagogy to Latin American countries, with a focus on stomach illness.

'Stomach cancer is very common in Latin America. But, when we make a list of the ten most common tumors in Europe, or even the USA, we can't spot stomach cancer. However, it is the second or third most common cancer in the world, because in countries like Ecuador, Peru, Chile and Paraguay it is much more frequent than colon cancer,' he pointed out.

The objective is to create a map of the different anomalies produced in stomach cancer and to touch on aspects of prevention, by using patient samples from participating countries including Chile, Paraguay, Argentina and Mexico, which all have a high incidence of stomach cancer. In Europe, the Netherlands, Portugal, Germany and Spain are also taking part and sharing their knowledge of the disease.

The program also includes training, with an online session run by experts every three months.

'It is a sort of community for dialogue and exchange of ideas. We are very excited and,' he said, 'I think it's going to develop well and bring extraordinary possibilities.'

With almost 24,000 members, 45% of them from outside Europe, ESMO is now a global forum for medical oncology.

## Education, fair distribution and sustainability as key axes for ESMO

A priority for Cervantes, who will serve as the society's president in 2022-2024, is education and training. The pace of knowledge is advancing at such a rate that professionals have to completely reassess every six or eight years. 'At various stages over the course of one's career, there are certain areas of knowledge that develop further and take us to new places,' he observed. 'As a professional society, we are responsible for educating our members.'

Inequity in the distribution of resources and access to fundamental medicines is also high on ESMO's agenda. Medicines that cure tumoral illnesses and cancer exist, but are not always available everywhere. Even drugs that have shown efficiency for decades, and have a reasonable price, are not always on offer.

ESMO has been working on a tool to better measure the clinical impact of drugs to help improve their fair distribution worldwide.

'We have medicines that brought great benefits when they were produced in the 70s. Maintaining their production and availability is fundamental. This requires a dialogue with the World Health Organisation, the EU and the regulatory agencies. It also requires a defined public policy structure.

'We have worked on a clinical benefit magnitude scale. When the authorities approve a new drug, our tool measures the impact of the benefit it will have on society. It is not just about whether one medicine is better than the other, but how much better, how many more patients will be cured, how many will live longer after two or three years of treatment,' Cervantes explained.

The clinical benefit magnitude scale classifies medicines according to how much they improve survival. The scale will help raise the bar with industry partners, Cervantes believes. 'Simply having this ranking,' he added, 'will motivate the industry to generate better medicines.'

Last but not least, ESMO will tackle the sustainability of the healthcare system, notably by incorporating evaluation tools that measure efficiency. 'My dream is to generate a global society in which professionals everywhere can understand and support each other, a platform that attracts knowledge and science, enabling us to deliver it as quickly as possible to patients,' he concluded.

**Andrés Cervantes** is Professor of Medicine at the University of Valencia and heads the Department of Medical Oncology at the University Hospital in Valencia, Spain. He is also scientific director of the Institute of Health Research INCLIVA, one of that country's nationally accredited research institutes. Cervantes completed his Medical Oncology training at Valencia's University Hospital and received a two-year research fellowship at the Free University Hospital in Amsterdam, where he obtained his PhD degree for work on multidrug resistance in the Cellular Pharmacology Lab of this institution under the mentorship of Professor Bob Pinedo. Cervantes is currently Chair of the Educational Committee and Transitional Director of Education, with a seat on the ESMO Council and Executive Board. He will be ESMO president for the term 2022-2024.

*Anaesthetic trainee trains traine*

# Portable POCUS impresses Zambian medics

**Consultant and trainee anaesthetists from Surrey, in the United Kingdom, have travelled to Lusaka with a Fujifilm SonoSite point-of-care ultrasound (POCUS) system, to train Zambian colleagues in ultrasound-guided regional anaesthesia. Here, Dr Madankumar Narayanan describes the educational objectives of the visit and the enthusiastic response from doctors there, as the team demonstrated the benefits of ultrasound-guided interventions in classroom workshops and on real patients.**

Anaesthetists from Surrey successfully ran POCUS workshops in Lusaka to train Zambian colleagues in ultrasound-guided regional anaesthesia

**Anaesthetic trainees** in the UK often undertake an "out-of-programme" fellowship to developing countries to expand their clinical and professional experiences. One such trainee visited the University Teaching Hospital in Lusaka for his fellowship and saw the challenges and limitations of managing patients' pain without the use of ultrasound-guided nerve blocks. On his return he decided to rally the support of his UK colleagues and arrange a training visit, to show Zambian anaesthetists how using ultrasound for vascular access and administering nerve blocks could transform care for their patients; he knew POCUS would significantly improve the pain management currently being offered. Three consultants and one trainee could commit to this project and linked up with two British trainees already in Zambia on fellowships at the time.

The team at the University Hospital using POCUS to assess a patient

## Well-equipped to introduce ultrasound

The University Teaching Hospital in Lusaka is the largest, most advanced hospital in Zambia and was a logical starting place for the training initiative. A seven day visit was planned – two days of classroom teaching, four days practical training in theatre and a day of consolidation. The team from the UK was equipped with a portable, robust SonoSite point-of-care ultrasound machine, donated for the training exercise, as well as for the Lusaka hospital to use in the future.

Anaesthetists at the University Teaching Hospital in Lusaka were unfamiliar with POCUS and did not have access to any machines. While their knowledge of anatomy was good, the process for choosing vascular access sites was based purely on clinical landmarks and they had used very little ultrasound in their diagnostic evaluations or management of pain – most of the theatre anaesthetists had never even seen nerve blocks performed. There is also very poor availability of pain-relief medication in Zambia; post-operative patients were having to tolerate significant levels of pain, which often increased their length of stay in hospital.

This presented huge scope to train the theatre anaesthetists to perform ultrasound-guided nerve blocks and introduce a culture of making a real difference in the quality of care they could provide their patients.

## Delivering training

The UK team carried out a preliminary workshop for 20 anaesthetists from across Zambia; comprehensive reading material was provided beforehand to outline the context of ultrasound-guided regional anaesthesia and cover the theoretical basics. Although the workshop was in a classroom setting, its content was very practical, concentrating on demonstrations of how to use the machine, how to hold the needles, how to scan and most importantly, how to guide vascular access and identify individual nerves. Four theatre anaesthetists from the workshop were then selected, all of whom worked at the University Hospital, and provided with hands-on training on real patients in their theatres. This initially focused on simple, low-risk nerve blocks – femoral, fascia iliac, axillary and popliteal – to help them improve their confidence, and then moved on to some more advanced blocks. They

*Mobile hybrid solution for cardiovascular procedures*

# Fast forward for C-arm users

**'Since 1972 Ziehm Imaging** has been a company of firsts. Our forward thinking has allowed us to be the mobile C-arm expert worldwide. As an innovation leader, we were the first manufacturer to show a Digital Subtraction Angiography (DSA) on a mobile C-arm, the first with a touchscreen user interface, the first with a flat-panel detector on a mobile C-arm, the first to launch a 3-D C-arm with flat-panel detector on the market and the first to introduce a mobile full-size C-arm with a CMOS detector.'

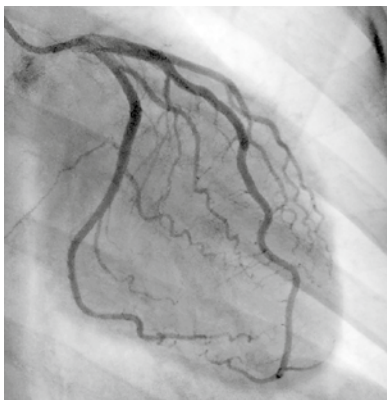
Thus Ziehm Imaging is proud to report the firm's past and continuing advances. 'We pursue new technologies long before they are established on the market. Our constant curiosity and forward thinking pay off. As an innovation leader, we are committed to our mission of setting new technology standards. We are always ahead in helping you meet your individual goals.

'Our portfolio offers answers to current challenges in the field of mobile imaging, such as new areas of clinical application, optimal workflows, patient safety, and cost-effectiveness.

## Reducing overall expenditures

'Thanks to the intraoperative use of our advanced systems, the accuracy of clinical outcomes can be improved, revision surgery rates significantly lowered and overall health expenditures reduced. The innovative use of our C-arms opens new clinical pathways and offers lower purchase and installation costs as well as a faster return on investment than fixed installed systems.'

The Ziehm Vision RFD Hybrid Edition represents a group of optional hardware and software that creates an option package on the device named Ziehm Vision RFD. 'The powerful 25kW mobile C-arm is designed to successfully perform during highly demanding interventional cardiovascular procedures,' the company reports. 'To ensure consistent system temperature and prevent system failure due to overheating it is ideally equipped with Advanced Active Cooling (AAC).


Advanced cardiac interventions

'Unique to the market, Ziehm continues, 'the system offers motorisation of all four axes for easy control directly from the sterile field. With its small footprint compared to a fixed installed system, this mobile solution delivers reliable results for complex applications, such as TAVI angioplasties and EVAR.

'Besides supporting clinicians in the daily routine, the Ziehm Vision RFD Hybrid Edition prevents revision surgeries resulting in shorter hospital stays and cost savings.'

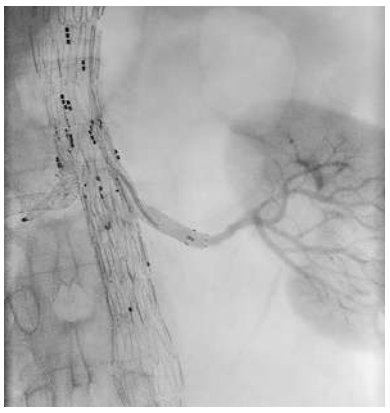
This system can instantly convert a conventional operating room into a hybrid room, the firm points out. 'It requires no modifications to the OR and is up and running in no time.'


Comprehensive mobile hybrid solution: Ziehm Vision RFD Hybrid Edition

## Extended vascular surgical capabilities

'Specialised vascular workflows and innovative software features meet the needs of complex vascular procedures and consequently save precious time in the OR,' Ziehm adds. 'Combined with excellent CMOS image quality, the system is a valuable contribution to any clinic's competitiveness and financial performance.'

The high-end system is also suitable for minimally invasive cardiac procedures, such as percutaneous transluminal coronary angioplasty (PTCA), heart valve implantations and pacemaker interventions. With its small footprint, it supports efficient room utilisation and exact results at manageable personnel costs.'


Extended vascular surgocal capabilities

were also instructed in submitting a maintenance and learning log to encourage them to develop their skills further after the team had left.

### Response of Zambian doctors

The beauty of the SonoSite ultrasound machines, particularly in this kind of scenario, is that they are extremely intuitive and 'non-threatening' to those who have never used POCUS before. They can withstand plenty of use and occasional unintended knocks or drops, and are incredibly user-friendly, which encourages continued learning and use of the machine in the first instance.

The presets are also very helpful and crucially, within a few minutes, the Zambian anaesthetists could correlate what they could see under ultrasound with what they already knew about anatomy, and quickly realise the benefits of clearly visualising important structures. Their excellent understanding of anatomy stood them in good stead for quickly progressing to use ultrasound to guide their identification of nerves and veins; the knowledge gained from the initial workshop was immediately consolidated and drawn upon in the following day's theatre-based training session. After just two days of training, the local anaesthetists were very excited about developing the use of POCUS to manage pain, particularly for patients following limb trauma surgery. They could immediately see huge potential for its use across Zambia and plans are already in place for the four anaesthetists trained in theatre to teach others within the hospital.

### Continued collaboration in the future

Above all, the Lusaka project has been extremely successful in increasing awareness of POCUS for pain management across Zambia. Everyone involved is keen to continue the collaboration and the aim is to repeat the ultrasound training annually. The Zambian anaesthetists are enthusiastic to learn even more and develop their skills further; hopefully the word will spread to other hospitals in the country, they will start to see the benefits and be able to make the case for procuring more equipment and a proper infrastructure around POCUS.

The UK team is eager to continue supporting hospitals in Lusaka and across the country, and to ultimately improve the lives of Zambians living with pain.


**Anaesthetists from the University Hospital were provided with hands-on training on real patients**

*Portable imaging*

## MRI 'to go'

The world's first low-cost, point-of-care (POC) magnetic resonance imaging (MRI) system was presented by Hyperfine Research Inc. at the American College of Emergency Physicians (ACEP) Scientific Assembly 2019.

Twenty times less costly, 35 times lower power, and 10 times lighter than the most current machines, this compact, open-design scanner wheels to the bedside for direct patient contact, plugs into a wall outlet and operates via a simple user interface on a tablet – with no need for trained technicians, shielded electronics, or separate hospital facilities, making MRI available to bed-bound patients as well as billions in rural areas, etc.

It creates standard clinical contrast images as well as informative 3-D renders. Hyperfine is developing software that improves with each use via deep learning algorithms. 'Our cloud-based software development kit will enable third parties to create AI applications for our device,' added Jonathan Rothberg PhD, Founder and Chairman of Hyperfine Research. 'Ultimately, Hyperfine aims to facilitate stroke triage, continuous monitoring of unstable patients, and MRI guidance of surgical interventions.'

*Personalised imaging with standardised results*

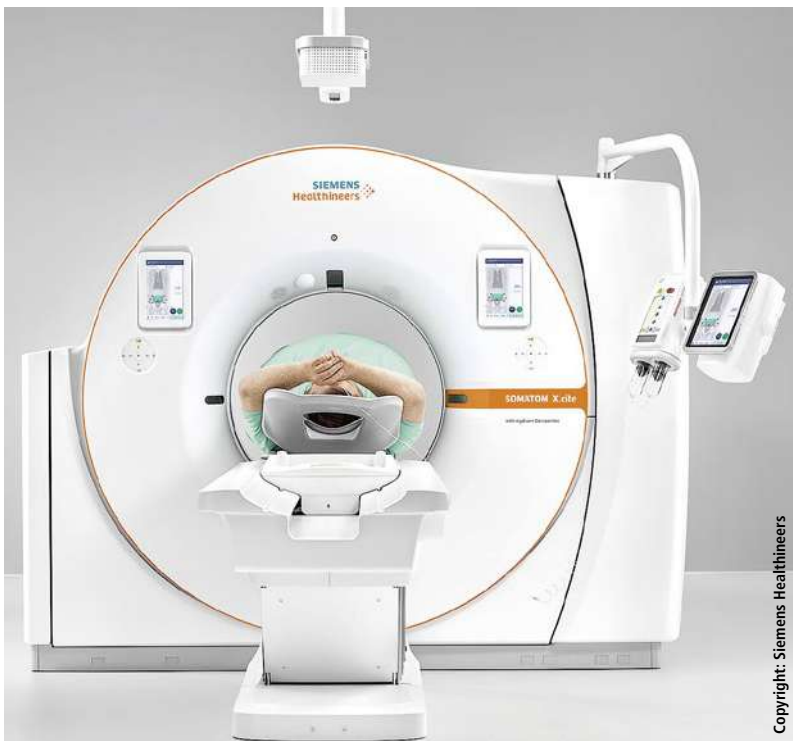
# Scanner protocols go automatic

**Against a backdrop of staff shortages, the ever-increasing demand for CT scans, and a need for lower doses for patients, Daniela Zimmermann reports on the new Siemens Healthineers Somatom X.cite single-source CT scanner and innovative myExam Companion user guiding system**

**With patient-friendly features** that also improve workflow and diagnostic accuracy, the new launch is coupled with the innovative myExam Companion – an intelligent user guidance system, which automatically adapts scanner protocols in line with patient data.

Clinically approved and available this month, the system has been tested by radiologists at several European hospitals, among them the University Hospital Zurich (UHZ), where it was unveiled at the end of November.

Professor Hatem Alkadhi, Consultant Radiologist at UHZ, described the Somatom X.cite as the 'one-fits-all' scanner in the way it unites first class image quality through high-end features; conducts complex examinations without problems; personalises imaging with standardised results and delivers workflow improvements.



Copyright: Siemens Healthineers

Somatom X.cite

## Investing in the future

Unveiling the product, André Hartung, President (Diagnostic Imaging), Siemens Healthineers, stressed that investing in the future was of utmost importance to Siemens Healthineers in a market where demand is soaring for high level healthcare solutions and the number of procedures rises.

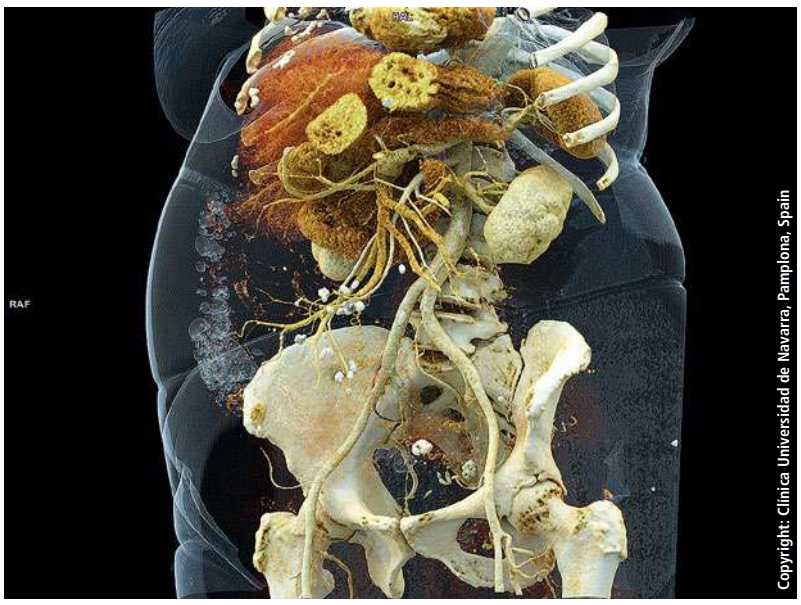
'Digitisation is at the core of addressing this challenge and, while more diagnostic data and information is being collected, we must ensure it is patient specific,' he said. This will see Siemens Healthineers invest in more software-based solutions with artificial intelligence (AI) and a high degree of automation at the heart of expanding the diagnostic offering.

He underlined how Somatom X.cite and myExam Companion are a big step in Siemens Healthineers' imaging portfolio toward the world of intelligent user support. The myExam Companion user guidance system, underpinned by AI, guides the user through the workflow using specific questions, making use of available patient data and combines these with additional patient-specific information gathered by asking specific questions, for example the presence of metal implants or a patient's ability to hold a breath. Accordingly, the scanner optimises the scan parameters.

With its 82cm gantry, Somatom X.cite can offer unprecedented image quality in the single-source segment combined with maximum patient comfort, Siemens Healthineers reports. Radiographers can prepare and perform the scan using removable tablets that are attached to the scanner using magnets, enabling them to remain alongside the patients until immediately before the scan, and then keep their patients in view via a 2-D camera integrated in the housing of the gantry while an optional 3-D camera gathers more information on a patient's anatomy and automatically positions them in the isocentre.

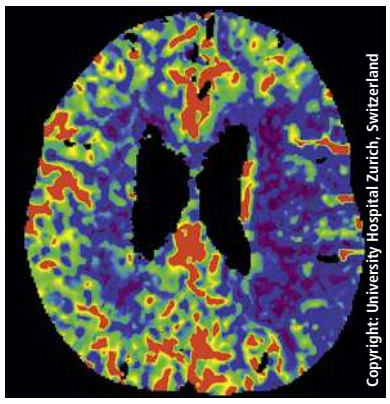
Dr Philipp Fischer, Head of Computed Tomography at Siemens Healthineers, said the healthcare sector was having to cope with a shortage of radiology staff with clinicians and technicians dealing with greater technical complexity under time pressures and often rotating between different modalities and systems, coupled with a demand for precision medicine with low dose and high image quality.

He explained how myExam Companion was an important step in helping offset some of that pressure and workload in the way it gathers data relevant to the exam with neither user interaction nor additional work steps. 'Before,' Fischer added, 'there were so many things that a technologist must do by himself to obtain data from different data sources. Now, this work will completely disappear.'



Copyright: Clinica Universidad de Navarra, Pamplona, Spain

Low kV imaging with high power reserves makes low kV possible even for bigger patients


Copyright: University Hospital Zurich, Switzerland

Stroke assessment Flex 4D Spiral

## Unique tools

Professor Christoph Stippich, Chairman of the UZH Department of Neuroradiology, outlined how his department had been testing Somatom X.cite with the new software platform with successful results.

Giving examples of imaging of the temporal bone and stroke and bleeding, he said the system had enabled reductions in radiation exposure and improved workflow and that the large gantry facilitates the examination of seriously ill patients.

Professor Alkadhi highlighted three features he felt added real benefits for patients and radiologists: Fast 3-D camera, Tin Filtration and myExam Companion. 'The 3-D camera is an important feature in placing patients in the right position,' he said. 'Studies have shown that 95% of patients were not positioned correctly, which is a problem and there are consequences as off centring affects dose.'

Research conducted in Zurich showed that off centring by 2cm can result in a 7% dose difference, while off centring by 4cm can result in a 20% dose difference.

'This is too much unnecessary dose,' he said, 'so we are very happy with the 3-D camera. We can show how the chest CT patient position is much more accurate when we use the 3-D camera, compared to manual patient positions.'

Topogram with Tin filtration, he pointed out, was also a way osef saving radiation dose and also highlighted the value of myExam Companion in workflow improvement and delivering standardised results.