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## RADIOLOGY

10-16

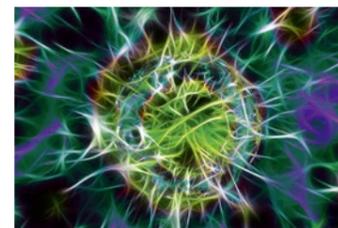
- Suspension for lighter radiation protection
- Deep learning, AI and big data
- Breast MRI data indicate metastases risk



## INFECTION CONTROL

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- Common sense beats infection outbreaks
- Non-commercial drug creation
- Links: social media and sexual infections



# VR eye goggles on prescription



Dr Todd Richmond is Director of the Mixed Reality Lab at the Institute for Creative Technologies (ICT), University of Southern California (USC) in Los Angeles, USA. A former chemistry professor, who incorporated multimedia and web technologies into his teaching and research, he moved to the ICT in 2006 where he currently leads the advanced prototype group. He works in areas of emerging disruptive technologies and their implications/ applications for training, learning, and operations; future environments for communication and collaboration; immersive technologies; interactive education; visualisation and analytics.

'Healthcare providers, just like educators, business leaders, and others, should view this emerging technology for what it is – a new medium for communication and collaboration that requires experimentation and time to understand and leverage,' Richmond advises. He also points to the ethical responsibilities associated with the medium and warns that product developers need to assume some sense of responsibility in the conversation around ethics.

Yet, VR offers great potential and 'can give clinicians a window into a patient that they would not otherwise have,' he said, pointing at Rizzo's PTSD clinical app as a prime example.

'It allows a clinician to quickly create a VR environment that mimics the memories of the patient.

While this helps the patient confront and work through previous trauma, and it also gives the clinician a visual image to go along with the talk therapy.

**As Virtual Reality plays an increasingly important role in healthcare settings, physicians could soon be writing out 'prescriptions' for such therapy, Mark Nicholls reports**

For many years, Virtual Reality (VR) has been part of the gaming sector with eye goggles for players to interact with certain scenarios. However, more recently VR has shown it can deliver specific treatments in healthcare. It is already being applied, for example, to treat phobias and as a distraction therapy for pain. Work also progresses on how it can enable better outcomes for invasive procedures or on-going treatments by lowering stress levels. Dr Todd Richmond, Director of the Mixed Reality Lab at the Institute for Creative Technologies (ICT) at the University of Southern California in Los Angeles, USA, explained: 'In the short-term there will likely be a lot

of work using VR as a distraction therapy, while longer-term we'll see VR used in more therapeutic roles. I predict that at some point in the not-too-distant future, physicians may be writing "prescriptions" for VR therapy.'

As one of the world's leading authorities on VR in a clinical setting, the USC lab has seen pioneering work in this area. His colleague Dr Skip Rizzo, ICT's Director for Medical Virtual Reality, has led a team to explore its use to treat post-traumatic stress disorder (PTSD) and other medical applications. In addition, in collaboration with Professor Leslie Saxon of the USC Center for Body Computing, his team has started looking at VR for stress reduction in patients about to undergo surgery.

However, Richmond acknowledges that they still need to explore what VR can treat, how it works, efficacy and any associated dangers.

**The Mixed Reality Laboratory has pioneered work on virtual reality**

### Treating a wide variety of mental health issues

Studies have already shown that VR can have benefits that meet or exceed current pharmaceutical therapies in, for example, pain reduction in burns patients, or psychological therapies such as PTSD.

'Due to the ability of a user to have cognitive embodiment in VR, there is a potential for treating a wide variety of mental health issues, phobias, and related issues,' Richmond confirmed. 'There is a more speculative potential for using VR to augment or replace drug regimens for certain types of treatments, and potentially 'rewire' neural pathways in constructive ways.'

The impact of wearables, implantables and biosensors also continues to spread from elite athletes – the first people to embrace these, to a

broader population. 'Having good biosensor data is still challenging, but the real hurdle is making that data actionable by the physician and individual,' Richmond added.

'There is a huge promise of improving elder/aging care through wearable, smart drugs, and other sensor systems. This is part of the broader question of the Internet of Things (IoT). Combining wearables, biosensors, voice agents (e.g. Alexa), and IoT again, provides the promise of more seamless healthcare, with the caveat that the real challenge is having the data tell a story that is actionable and will change human behaviour.'

### Experimentation required

However, he warns about rushing ahead too quickly with VR and other technology in a healthcare setting, stressing that the concept is still in the experimentation stage and does not provide 'immediate fixes to the ills of society.'



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# Healthcare data shake-up is imminent

Healthcare organisations across Europe are being warned to be ready for new laws that mark the biggest shake-up in data protection legislation in decades.

The General Data Protection Regulation (GDPR) will come into effect across Europe on 25 May and, despite the vote to leave the European Union, the British Government has confirmed that it will be enshrined in UK law on that date.

In the United Kingdom, key areas that the National Health Service (NHS) and other healthcare providers are urged to be aware of include issues such as what needs to be done to instil a privacy culture and how to avoid penalties – which include heavy fines.

## Understanding responsibilities

Whilst the new legislation affects a wide range of organisations and businesses, Freelance Data Privacy Consultant Darren Rose emphasises the importance of healthcare providers being ready for the change. He explains that they need to focus on understanding the new GDPR privacy law and its possible implications;

understanding the organisation's responsibilities as a Data Controller; dealing with Data Processors; understanding Data Subject Rights, and identifying sensitive personal data. Additionally, they must be aware of and understand locations and storage methods; Personal Information Management Systems (PIMS); Information Security Management Systems (ISMS); risk and risk mitigation; register breaches and the process of reporting a breach to the supervisory authority.

When the GDPR becomes law, Rose warned, organisations and firms need to be aware of the possible heavy fines, subjects' right to compensation, a new specific consent with evidence and rights to withdraw consent, and mandatory privacy impact assessments, mandatory documentation of compliance and mandatory breach notifications within 72 hours of discovery.

'I also draw organisations' attention to the potential impact of loss



of reputation or judicial remedy for the data subject, which can be far reaching, even if the local supervisory authority chooses not to impose a fine on the organisation,' Rose added.

## Focus on the human factor

While there are stricter rules for gathering and storing sensitive data as well as increased powers for regulators, he believes this should not have a major impact on the health and social care sector as the 'fundamental principles upon which data is gathered, transported and processed' should already be at the heart of the organisation.

'Individuals already responsible for delivering data protection readiness will be very aware of the current,' he said.

'But, within the context of health and social care, organisations should take particular note of the inclusion of biometric (retina imagery) and genetic data into the special categories as well as changes to sharing of data for medical research purposes and the correct use of anonymisation.'

Organisations, regardless of their sector, must understand the importance of training and awareness as the cornerstone of a privacy

UK's NHS tests management systems

# Digitally controlled beds and patient pathways

Digital bed management systems to improve patient flow are being tested in National Health Service (NHS) UK hospitals and are showing early signs of success. Innovations such as patient tracking and real-time location of equipment and staff to improve hospital efficiency are being tested at 10 sites.

Leading the project, Bernard Quinn, Director of Improvement Programmes for NHS Improvement, is particularly optimistic about technology that monitors bed availability and patient flow. 'Every winter, to meet added pressures in the NHS, an additional 3,000-5,000 beds go into the system but we don't often look at the 100,000 beds that are already there, in terms of how effectively we are using them,' he explained.

The UK has half the hospital beds it had in 1987, but sub-optimal flow still sees 95% occupancy rates. The global trend is for fewer hospital beds with the latest data showing that of the 32 OECD countries, 90% are reducing bed numbers.

The USA, Denmark and Sweden appear to be making better use of their beds via flow systems and this has inspired the NHS – which treats 351,000 patients a day – to focus on making improvements.

'Since the 1970s,' Quinn notes, 'industries such as car manufacturing have shifted from labour-intensive to computerised systems but over that same period our way of managing flow has not changed.' Convinced that digital flow tools will improve the efficiency of patient movement in hospitals, he said the NHS is now seriously assessing at a range of systems from various



The control centre allows staff to oversee and intervene if a patient is off track

manufacturers for what the NHS needs. Some are for bed management, focusing on flow from emergency departments to wards, while others also take in theatres, radiology and pharmacy.

## Mapping the patient pathway

Because there is a goal of closer cohesion between health and social care in the UK, the NHS is eyeing systems that bridge the gap between hospital, community and nursing home environment, a step that may positively impact down on the issue of delayed discharges with patients blocking beds before being moved to the next step of their care.

Digital bed flow systems map a patient pathway throughout the hospital with various key stages highlighted. This cuts out numerous phone calls and means key personnel can access it via real-time wall-boards in A&E, on wards and in

physiotherapy, pharmacy and theatres to track a patient's whereabouts and what is needed to deliver their stage of care on the pathway.

'If you couple it to a centralised admission/discharge function with a control room you can coordinate placement of patients with the available beds across a whole hospital as well as a group of hospitals,' Quinn added.

'With the cascade of intelligence that comes out of that, you have a better chance of getting the right person into the right bed first time and can reduce delays in the care process that can occur when manually co-ordinating care from multiple departments.'

Benefits cited by manufacturers include reduced A&E times and length of stay, better matching of staff skills to patients, and reduction of 'dead bed' time when one patient has left the bed before another occupies it.

In some NHS hospitals this can be up to six hours but the Countess of Chester Hospital in north-west England says the Real-time Locating System (RTLS) it is testing has cut that from four to two-and-a-half hours, while the Luton and Dunstable Hospital – often the best performing in the UK for A&E wait time targets – says it would be impossible to hit those targets without the digital flow system. The Royal Wolverhampton Hospital – the first to trial the more expensive RTLS – reduced A&E breaches and also did not need to open additional wards this winter.

## Readjusting the focus on patient care

RTLS sees tags on patients, equipment, such as pumps and pressure mattresses, as well as in staff badges. 'It helps match patients to the skill set of staff, but also means

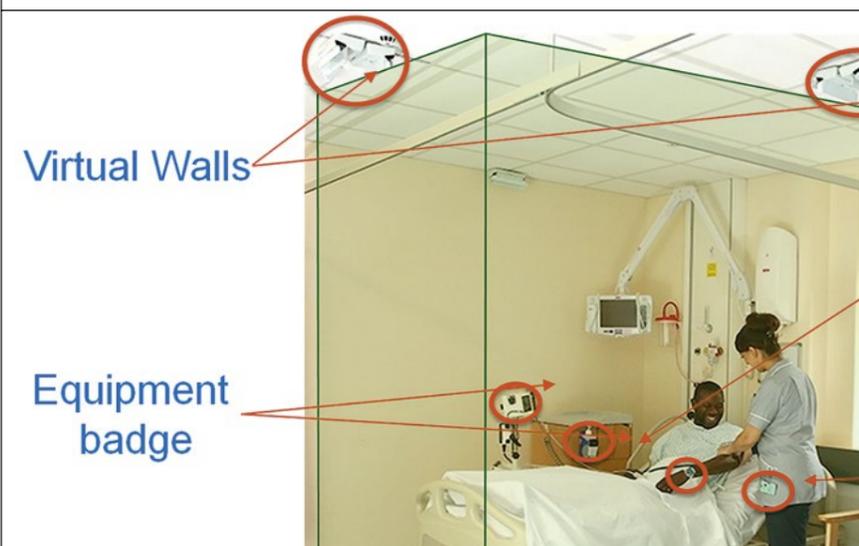
RTL systems provide tags for patients, staff and equipment, to help match patients to staff's skills, as well as reduce time spent looking for appliances

staff not chasing after pressure mattress and pumps because they have a system that can tell in real time exactly where something is because they are asset tracked.'

While the centralised admissions and discharge element – with a main control room – may remove some of the autonomy wards might have to decide who comes into their ward or not, it does see nurses released from logistics and cleaning to focus on core nursing and patient care.

Quinn, who is keen to hear from other European hospitals that have used digital flow systems, said: 'Along with Department of Health, NHS England and NHS Digital, we are jointly looking at what approach we might take from these systems, what the options are that make it affordable for the NHS, and whether a national specification might be a route to go down. At the moment there are different systems in different hospitals and we have not yet settled on the best specification.'

While academic research in the field is limited, the NHS is working





**Darren Rose** is a Freelance Data Privacy Consultant/Trainer. A lead education consultant, he is a member of the International Association of Privacy Professionals (IAPP) and has been providing data handling consultancy and training, to education for almost a decade through his roles as SIMS Consultant and school compliance advisor.

culture, Rose advised, because the human factor is often overlooked when it could be the simplest risk to address.

'Within the social care element,' Rose also cautioned, 'I advise particular attention to the quantity of sensitive data being transported and shared between organisations, especially within the elderly care context, including medical notes between residential care and health-care providers for appointments, social work and the mental capacity assessments.'

MN



**Bernard Quinn**, Director of Improvement Programmes for the UK's NHS Improvement, leads these projects across emergency departments, elective care, theatres and out-patients, as well as the digital area that aims to improve flow. His earlier career has included work in the Government's Cabinet Office, several NHS executive roles and in clinical commissioning.

to produce qualitative data on the benefits of digital tracking.

However, Quinn believes a strong and clear message is emerging that the digital bed tracking approach is the direction NHS hospitals need to go. 'It is not a matter of if,' he said, 'it's a matter of when and, by engaging with this early, I think we can define a specification which will allow flow across a wider hospital environment.'

MN



Patient badge

Staff badge

Korean concepts show strengths among over 1,300 exhibitors

# The 34th KIMES 2018



Hyun Chul Oh, marketing and sales director Exoatlet, presents the robotic exoskeleton



This year's event became the largest in a 34-year history



Hyung Seok Kim, CEO mobiU, demonstrates the use of EZpole – a wearable IV pole

## Report: Callan Emery

Held in Seoul, this March, the 34th annual KIMES (Korea International Medical & Hospital Equipment Show) proved to be the largest in the event's history, hosting 1,313 companies from 34 countries.

Achieving this milestone clearly demonstrates the increasing significance of this show to the world's leading medical device manufacturers and service providers, who recognise the importance of KIMES as a major platform for presenting their products to the Korean and East Asian markets.

As well as the many foreign exhibitors – 117 from the USA, 165 from China, 90 from Germany, among many others – there were, of course, Korean companies, including several leading global firms such as Samsung and DK Medical Solutions.

Additionally, according to Korea E&EX Inc. the KIMES organisers, more than 3,500 foreign buyers attended the 2018 event, underlining a growing significance of Korean medical devices in foreign markets, a key reason for the event itself – i.e. to promote exporting of the coun-

try's own medical devices. Having spoken to several Korean companies at the event it is apparent that they are raising the bar in terms of quality and prices and want to provide strong competition to more well-known and established companies in the West.

## Robotic help for rehabilitation

A case in point is the Korean firm Exoatlet, which has developed a robotic exoskeleton for rehabilitative walking assistance. Hyun Chul Oh, marketing and sales director of Exoatlet, explained that the device offers 24 modes to suit a variety of patient gaits – long step, short step, etc. 'The exoskeleton is currently being used in 40 Korean hospitals as a test bed,' Oh said. It is now on sale there and will be marketed this year in several other countries. 'We have contracts with hospitals in Singapore, Malaysia and Thailand,' Oh added.

'We will open subsidiaries in China, Japan, Europe and the US later this year,' he said. 'We expect to complete our CE registration by the end of this year.' He further

explained that the exoskeleton can run for eight hours on a single charge – 'the whole day, which is important for commercialisation purposes. In a single day, one system can be used for many patients ranging between 150-190 cm in height and up to a maximum of 100kg in weight.'

## Focus on practice-oriented innovations

At the KIMES opening ceremony, the director of Korea E&EX Inc. said that, when looking over the estimated 30,000+ products on show and comparing this with previous years, he noticed a definite swing in innovation from imaging machines to robotic devices. Exoatlet's exoskeleton is one example.

However, as well as the advanced robotic and imaging devices there were also a number of quite simple, though ingenious novel medical devices on show. Among these is the EZpole developed by the small Korean firm mobiU. The EZpole is a cleverly designed, simple pole to attach to a patient's shoulder and hold up an IV drip. The patient wears the device when walking

around, enabling independent mobility while still receiving an IV drip. Hyung Seok Kim, CEO of mobiU, remarked that by improving a patient's mobility, recovery could be speeded up.

Another smart device launched at KIMES 2018 is a portable auto needle removal instrument (NRI-15M) developed by Korean company Hastechnology. This device was developed to prevent needle stick injuries, a common healthcare hazard.

The NRI is simple to use. A healthcare worker places the used syringe with needle into the device. The device cleanly snaps off the needle from the syringe and collects the used needles in a container that can then be easily and safely discarded.

The NRI has an LCD screen with indicators to keep track of the current state of separation of the needle from the syringe and alerts healthcare staff when the needle container is full and ready for disposal.

In conclusion, KIMES 2018 was a hugely frequented showcase for innovations that aim to become even stronger in international markets.




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# Increasing knowledge of rare d

Two major projects feeding on big data and based in Spain have recently come under the spotlight: Mendelian, a tool to expedite rare diseases diagnosis, and Harmony, an EU platform that aims to improve targeted therapy in haematological cancer, Mélisande Rouger reports

Rare diseases affect as many as 6% of the Spanish population. Although this percentage is high, these conditions are individually rare, which complicates and often delays treatment, according to Ignacio Hernandez Medrano, a neurologist at Ramón y Cajal Hospital in Madrid. 'There are more than 10,000 reported individually rare diseases. As a physician, maybe you will meet one such pathology in your career, and when you do, you won't know what it looks like.

## No human could possibly read through all the data

A few years ago, Medrano founded Mendelian, a search engine that collects and sorts out knowledge of rare genetic diseases to accelerate their diagnosis. Diagnosing rare diseases currently takes 7-10 years, mainly because finding information on the disease itself can prove extremely long.

Thousands of public databases are available on the Internet, with information uploaded by experts in the field, but no human being is capable

of reading through all this data.

However, a tool that uses big data can, Medrano explained. 'We use technology that can cope with huge amounts of data on gene variants, clinical features and other information, and filter them by items that are clinically relevant, all the while taking into account the biochemical routes,' he said. 'Once our platform has gathered all the results and put all the data together, it runs algorithms to sort out relevant information for the clinician.'

Mendelian is proving to be quite accurate. Out of a selection of 20 at risk genes selected by the platform, one turns out to be the gene causing the disease, on average, according to Medrano. Interesting results have also been found using the platform; for instance that genes may be causing diseases only because they are related in nature and physiology, even though no previous research has showed so. The young company is now trying to benchmark its services comparing synthetic patients against real patients, who have previously been diagnosed.



Around 5,000 people have visited the platform each month over the past six months, most of them being geneticists, paediatricians, internal medicine physicians and specialists from every discipline. Medrano expects this number to grow, as the platform will become available to patients as well, and when genetic blood tests will become more generally available.

The entire Harmony team

## Boosting targeted therapy in haematological cancer

In the era of next-generation sequencing and genetic knowledge of the genome and cancer genome, data must be gathered to better characterise disease and improve targeted therapy, according

to Jesús María Hernandez Rivas, a leading haematologist at Salamanca University Hospital.

Rivas is coordinator of Harmony, a European platform for the study and discovery of the most efficient treatments for haematological malignancies. The platform is part of the Innovative Medicines Initiative (IMI2), and aims to assemble all the stakeholders in the field and set up

A family doctor questions the psychological issues behind testing

# What do tests do for doctors?

Figures show that the rates of pathology testing are continuing to rise despite a backdrop of financial constraint within the NHS.

General practitioner (GP) Dr Jessica Watson has expressed concern that some tests are being carried out for the wrong reasons – often for a non-medical purpose – and that unnecessary tests are causing increased anxiety and uncertainty rather than offering reassurance for some patients.

Having researched this area extensively, at the FILM 2018 – Frontiers in Laboratory Medicine conference in the UK this January her presentation focused on 'What do tests do for doctors? Over-diagnosis and the psychology of testing'.

## Over-zealous use of blood tests

The conundrum faced by family doctors is 'to test, or not to test'. Watson, who is also a NIHR Doctoral Research Fellow at the University of Bristol, said: 'It's a fascinating question as a researcher, but more importantly as a clinician. While medical reasons are important, what fascinated me are the psychological reasons for testing.'

Concerned that such psychological reasons for tests may be fueling over-testing and over-diagnosis, she expressed increasing concern that over-zealous use of blood test investigations could actually lead to patient harm. However, she also acknowledged that doctors often face the difficult balance between

deciding whether to test or as they try to uncover underlying disease.

She pointed to variability in testing rates across the UK with areas of over-testing and areas of under-testing and suggested that both can cause patient harm. Additionally, there is the issue of how to avoid over-diagnosis, which may divert resource from more effective interventions, generate waste and inequalities and increase the workload of primary care.

As part of her research outlined to delegates, she discussed interviews she had conducted with a selection of GPs about blood tests performed, and explored their motives for carrying out the blood tests.

## Fear of neglect

This ranged from fulfilling non-medical roles such as a 'gift' to the concerned patient in return for perhaps not taking antibiotics, for example, or used as a bridge to build a 'therapeutic alliance' with a patient in an attempt to lead towards better patient management.

But conducting tests also managed uncertainty for the GP with fear of missing something being a common driver, as well as fear of litigation. 'The role of the blood test can be to manage uncertainty,' Watson said, 'but, paradoxically, inconclusive test results can create anxiety and uncertainty.' From there, it can lead to more tests and stress and create the 'investigation momentum' where further tests are constantly being sought



Dr Jessica Watson is a general practitioner (GP) and NIHR Doctoral Research Fellow at the University of Bristol in the UK with an interest in how GPs use tests in primary care. Her PhD is looking at inflammatory markers to detect inflammation in the blood. Watson's research sets out to describe the probability of various diseases given the test results in primary care. She is a member of Bristol Population Health Science Institute, NIHR CLAHRC West, Bristol Medical School (PHS) and Bristol Doctoral College.

in the relentless pursuit of unachievable certainty. Equally, normal test results can at times do little to reassure a patient. 'While the unit cost of a blood test is relatively small, the downstream cascade of testing can be significant.' Guidelines have also posed GPs problems because many patents do not necessarily fit guidelines, Watson continued. The importance of shared decision-making over tests, she pointed out, may lead to reduced testing, or even patients opting not to have a specific test.

However, she noted that required time and resources in explaining the benefits to a patient, evidence, education and an acknowledgement that uncertainty is inherent in testing. While defining unnecessary blood testing is not as simple as developing medical criteria and guidelines for testing, Watson concluded: 'Over-testing harms patients, leading to a rising workload in general practice and rising costs for the NHS.' MN

# Monitoring blood cells

A thin copper wire wrapped around a channel slightly thicker than a strand of hair could be the key to manufacturing a compact electronic device capable of counting white blood cells from the comfort of one's home, according to engineers at Kennesaw State University in Georgia, USA.

Hoseon Lee, an assistant professor of electrical engineering in the Southern Polytechnic College of Engineering and Engineering Technology, and his team of six students, have spent the past year researching more efficient ways for chemotherapy patients to monitor their white blood cell count without frequent, and sometimes costly, visits to the hospital. As cancer treatments often lead to lower white blood cell counts and an increased risk for infection, regular testing to measure levels is necessary, according to the Mayo Clinic.

To monitor white blood cell levels, many clinics use the flow cytometry, method, Lee said. The process works by dying cells a fluorescent colour which are then illuminated by a laser. As the dyed cells pass through a narrow channel, the scattered light and fluorescence emitted are detected, indicating an object is there.

Although this technique can provide many levels of insight into a patient's health, the equipment is bulky and expensive, limiting its portability. 'Flow cytometry equipment can perform lots of different functions: it can sort the cells, count them and do other things that aren't entirely necessary for every patient', Lee said. 'If we can focus on one thing – counting cells – we can make something smaller and more affordable for

gnosis and cancer therapy

# Diseases

a data repository to gather all the knowledge acquired across the EU.

'Having such a repository will help ensure that we are using quality data. Patients with leukaemia or lymphoma are complex cases, and we produce a huge amount of data on these diseases. However some of this data is not easy to manage or may not be relevant,' Rivas said.

International studies that have a comprehensive approach are the best way to advance knowledge of rare malignancies, Rivas explained, and Harmony has the added value of involving all stakeholders in haematological tumours, including the industry, which funds 50% of the project, and patient groups.

### Collecting results in the EU

'These type of studies cannot be conducted on a national or regional level, and they must include everyone who is concerned,' he said.

'We can have a general idea of what is going on in Spain by using data from cooperative groups, but the prevalence of these diseases is so low that we don't have enough patient data. By using only your own data you can publish in scientific journals, but the reliability of your results is not strong enough.'

The Harmony researchers are therefore collecting impacting results in every European Union country, a task made easier since cooperative groups such as Pethema and Geltamo in Spain, Gimema in

Italy, Hovon in the Netherlands and MRCI in the UK have already sorted out the data nationally.

This experience on the local level will help ensure European researchers sort out meaningful data on patient characteristics, an important factor in finding new cures, and which could prove more significant than any other findings, the haematologist said.

'Finding a way in which we can define clinical, biological and molecular patient characteristics will be much more important than

any other outcomes. Every time the industry launches a project, it needs a new database, with new data collection,' Rivas explained.

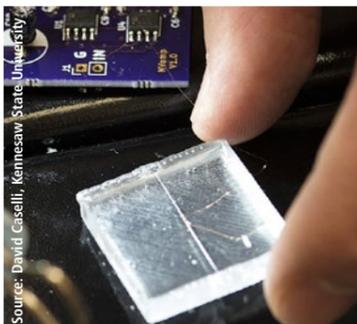
'Just putting together all the data from different projects inside a repository will help tell stakeholders what parameters they need to include depending on the disease they are working on.'

However, heterogeneity of sources is a challenge during big data collection, and data harmonisation will be paramount for the years to come, he concluded. ■



Neurologist **Ignacio Hernández Medrano** (above) at Ramón y Cajal Hospital in Madrid, Spain, was elected one of the most influential healthcare professionals in 2016 by the specialist press for his work in HC systemic change using IT and big data.  
Haematologist **Jesús María Hernández Rivas**, coordinates the European Union Harmony platform at Salamanca University Hospital

## g white s at home



With no bulky machinery or hospital trips necessary, the tiny white blood cell counter has the potential to make patients' daily lives easier

both the patient and the provider.' To decrease the weight and size of their device, Lee and team created a prototype that can operate on two AAA batteries, rather than a power outlet. It uses a coil wrapped around channel just 100 microns wide, which is large enough for two to three blood cells to pass through at a time. The channel is suspended in a small block of silicone gel, and the coil leads to a circuit board built by electrical engineering students to receive input as cells pass through the channel. While most flow cytometry machinery need a table, the device the team built potentially could fit in one hand. To count cells, the team attaches a magnetic nanoparticle to white blood cells by mixing the two in a vial. As magnetised cells pass through the coil, a flux in voltage is detected and logged on the circuit board. Each spike in voltage signifies a cell passing through the coil, providing a readout of white blood cell levels. The overall design is still being, but Lee has filed for a patent and hopes for future developments. ■

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Meeting the challenge of modern laboratory demands

# Utilisation Management Tools bring benefits



Faced with the constant challenge of increasing demand and a backdrop of falling reimbursement, the Mayo Clinic in the USA has adopted an innovative and proactive approach to managing its laboratory services. This has seen the US-based medical giant embrace a variety of tools and reference materials to aid clinician

For an organisation such as the Mayo Clinic, which conducts 25 million tests annually, it is important to achieve value based care, Curt Hanson believes

decision making, improve care and lower costs.

During the FiLM 2018 – Frontiers in Laboratory Medicine January

conference in Birmingham, United Kingdom, Dr Curt Hanson, Chief Medical Officer of Mayo Medical Laboratories at Mayo Clinic, Rochester, outlined the organisation's approach, including procedures implemented to guide appropriate test ordering and education packages.

A key element lay in harnessing big data to help better inform the testing profile of Mayo Clinic, while continuing to cost-effectively meet the needs of clinicians and patients.

It was ever more important to achieve value based care, he said, particularly in an organisation such as the Mayo Clinic, which conducts 25 million tests annually; but he stressed there were multiple components to consider. 'To add value, you must move beyond thinking about cost effectiveness and think about clinical effectiveness. You have to think about the impact it has in terms of confidence in patient care.'

## Big data can help to evaluate test effectiveness

In his presentation – Demand utilisation – the Mayo Clinic approach – he said big data was critical in understanding populations.

However, he warned: 'We have to remember that databases are not necessarily designed for our purposes but getting access to them can really help us to move towards

understanding value in the lab.' With tests such as ESR v CRP, for example, big data can highlight information that can help work out the relative value of such tests. 'It gives an opportunity to look at routine tests and an opportunity to flush out waste from the system,' Hanson said, adding that it can also look at test usage and effectiveness to work out internal guidelines on testing, and see what savings can be made.

He pointed to Clinical Decision Support Tools and Utilisation Management Tools, used by the Mayo Clinic, and effective in other settings, as having clear benefits but stressed the importance of laboratorians knowing how to use these tools. CDS tools can support frequency of tests, cost information, value-based testing, where there should be restriction on tests, and population health data, Hanson explained.

Utilisation Management Tools can provide clinician education, help decisions, make certain tests obsolete, restrict frequency of certain tests, review admission and treatment templates, look at physician profiling and report cards and establish a utilisation review process for the send-outs.

## Laboratory strategies need clinical input

Hanson also pointed out that using genetic counsellors to review high



**Dr Curt Hanson**, Chief Medical Officer of Mayo Medical Laboratories at Mayo Clinic, Rochester, USA, is a haematopathologist with a research focus on chronic lymphocytic leukaemia (CLL) and the myeloproliferative neoplasms (MPN). He has played a key role in the development of novel flow cytometry assays to detect minimal residual disease in CLL and the application of laboratory-based prognostic risk factors. Hanson is also a Consultant and Vice Chair (Extramural Laboratory Affairs) in the Division of Haematopathology, Department of Laboratory Medicine and Pathology at Mayo Clinic.

cost hereditary testing was a good move and that 'genetic counsellors more than prove themselves in terms of value'. From a philosophical challenge perspective with clinical laboratory utilisation, he warned that laboratorians must be 'comfortable with degrees of uncertainty'.

'I believe that, as laboratorians, we need to lead the way with utilisation management. We have tonnes of data, let us use that to reduce that waste,' he said. 'In addition, as laboratorians, we must get out of the office and think clinically. We have to think differently on how value based laboratory strategies can contribute to patient care and use big data and analytics to help drive laboratory-based initiatives.' MN ■

The earlier the better for a significantly improved outcome

# Tackling acute kidney injury

Steps taken by a New York health system to identify and tackle acute kidney injury (AKI) at an early stage are having a significant impact on improving intervention and patient outcomes.

Key to the turnaround lies in pathologists accessing big data from the laboratory, and working more closely with administrative personnel to identify early AKI and then responding to it more quickly.

Speaking at the FiLM 2018 – Frontiers in Laboratory Medicine January congress in Birmingham, UK, Tarush Kothari outlined how this had not only allowed patients to be treated more promptly at the network of New York hospitals where he works, but had also showed considerable cost savings and helped reduce excess hospital days related to AKI.

His presentation focused on augmenting administrative data with laboratory data to improve quality of care and enable registry-based clinical studies for AKI.

In his presentation Kothari, who is a Pathology Informaticist with Northwell Health Laboratories in the USA, discussed the clinical and economic significance of a quicker response to AKI.

## Progressing AKI increases hospital costs

Some 15-20% of all hospital patients have AKI – up to 30% in critical care

settings – yet many are treated by non-nephrologists. 'The economic significance is that it amounts to 5% of total hospital costs, a figure that is conservative by today's standards,' he pointed out. 'Also, it's increasingly recognised that AKI and Chronic Kidney Disease (CKD) are not separate conditions but more a spectrum of disorders.'

Mortality, length of stay, and costs worsen as AKI progresses from stage one to stage three, with an increased likelihood of CKD and renal replacement therapy costs, he said. Estimates put the total expenditure attributable to AKI in the USA at \$10 billion a year.

Addressing delegates to the congress, organised by the Association for Clinical Biochemistry and Laboratory Medicine and the Dark Report, Kothari highlighted a case study at the 250-bed Forest Hills Hospital in Queens, New York, where they found three to four cases a day of AKI leading to an excess stay in hospital of two days per case. 'That was a one million-a-year problem for just one hospital site,' he observed. 'So the idea is that, if you are able to prevent or diagnose this condition at an earlier stage, then savings throughout the entire hospital system would be enormous.'

A key issue is that AKI is often under-diagnosed and under-recognised, primarily through a lack of awareness among non-nephrologists and lack of effective Clinical Decision Support (CDS) tools leading to variable standards of care.

## Greater awareness through lab alert and training

The solution devised by Kothari's team saw the implementation of a real-time laboratory generated electronic AKI alert using a delta checking algorithm.

This sparked alerts involving 20 patients a day at Forest Hills Hospital. But having validated the

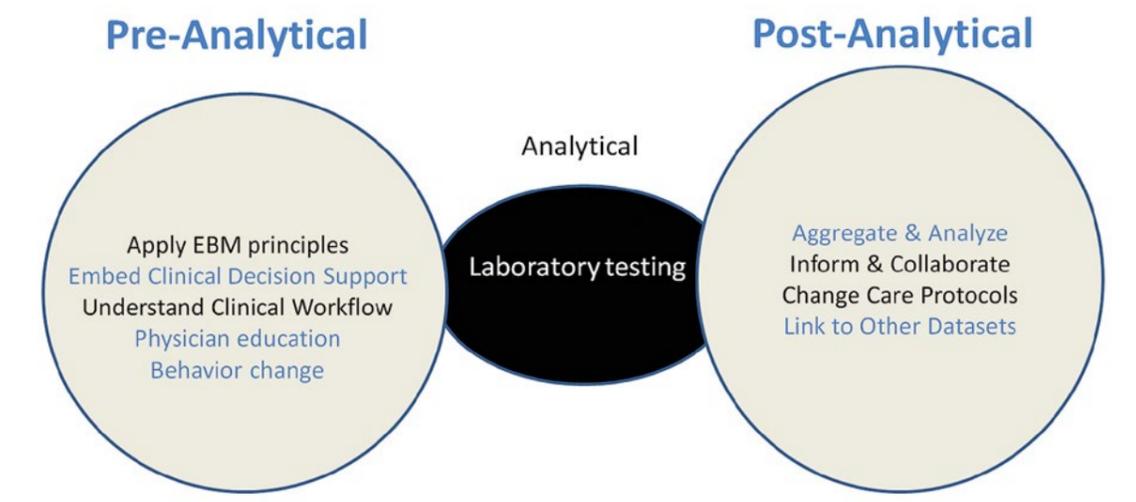
alert system as being correct, they began a physician education and awareness campaign and a daily reporting on AKIs for each 24-hour period during the first six months of the pilot in 2014.

That was extended to include partnering with the health information management team to improve clinical documentation and further education of physicians, nurses and medical coders.

It emerged that hospital administrative staff were not capturing the incidence and severity of AKI, but with further awareness the coding for AKI improved dramatically and seven additional hospital sites, where they were able to replicate the algorithm fairly easily, were added in January 2015.

The outcome was greater awareness of AKI among physicians and administrative personnel, and identifying the condition before it became serious and severe, and then implementing an effective treatment regime.

'Only laboratory creatinine data, at least in the case of AKI, can provide more granular information on disease severity, onset, chronicity, duration, recovery and long-term follow up of patients,' Kothari explained. 'It is not just how we process specimens and generate results, but also about laboratorians getting out there and talking to clinical colleagues.'



The status quo and recent developments in LC-MS

# Liquid chromatography-mass spectrometry

European Hospital has recently focused on the development of liquid chromatography-mass spectrometry (LC-MS) for use in analytical/medical diagnostics. Dr Stavros Kromidas, an expert in high-performance liquid chromatography (HPLC) and author of several specialist books, has published his latest book 'The HPLC-MS Handbook for Practitioners'. EH correspondent Walter Depner interviewed him about this and a new technique that enables MS analysis to be used live in the operating room (OR).

**'In your previous HPLC publications you described the theoretical principles in concise but sufficient and easily comprehensible terms, intending the works for the practical user,' Depner began. 'The title of your new publication – for the first time dealing with chromatographic and spectroscopic methods – suggests the same focus. If this is the case, to whom is it addressed?'**

'Indeed, practical aspects take centre stage. While we do explain the background of the individual LC-MS modes, we tried to present more tips and recommendations for everyday use. The book is geared towards users in the lab and their managers, to the extent that the latter are interested in practical issues.'

**For decades, coupled LC-MS systems have primarily been used in life sciences and environment testing. When has this method started to enter the realm of healthcare?'**

'You have to clearly define what you are looking at: mass spectrometry has long been used in healthcare; a recent example is the so-called

Rapid Evaporative Ionisation Mass Spectrometry, REIMS for short.

'This technique allows us to recognise malignant tissue in real-time during surgery. 'An MS probe is attached to the scalpel with which the surgeon removes suspicious tissue. The hand-piece continuously collects mass spectra, which are analysed by a software package and the results – malignant cells or benign cells – are immediately reported back to the surgeon. 'This technique is apparently as reliable as the

Mass spectrometry has a long healthcare history



conventional, but much more time-consuming, histological analysis. In a lab performing clinical routine tests, however, LC-MS is rarely used, because the relevant values can be identified with simpler methods. In a research setting, by contrast, the technique is gaining ground since the boundaries between biochemistry, diagnostics and toxicology are increasingly blurred; case in point: OMICs technologies, monoclonal antibodies and biomarkers.'

**Apart from the field of applications, many aspects are relevant for all users. To what extent**

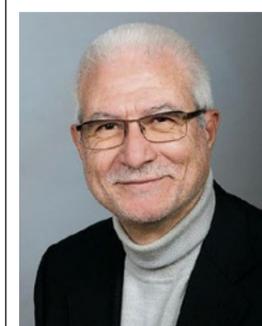
**have spatial, equipment and staff requirements for LC-MS use changed?'**

'LC-MS coupling has been done for 20 to 25 years and has taken off in the last seven to ten years. Thus the method can safely be called mature and well established.

'Spatial requirements are negligible since the equipment is rather compact. Nevertheless, two distinct trends can be observed: on the one hand there are simple, small and robust instruments for routine tasks where the target analytics are known. In these cases the users do not need special skills. On the other hand, you've got high-end equipment for non-target analytics. To be able to use the technology efficiently, the users need in-depth knowledge. Fortunately there are ever more new tools to assist users, such as online comparison with spectra libraries, the use of several and/or new interfaces and smart use of different data, e.g. retention times from orthogonal separations, spectra or log-D values.'

**A particular focus of your work is column technology and gradient optimisation. Do they significantly impact on coupling systems and if so what needs to be taken into account?'**

'Indeed, in LC-MS coupling stable stationary phases are required that do not "bleed". This is quite a challenge in the frequently required polar stationary phases. The manufacturers are busy addressing the issue, and phases with an additional positive load were introduced recently. Concerning the gradient, the principle naturally stays the same, but there are specific characteristics. These aspects are dealt with in a new book due out soon.\*'



Born in Thessaloniki, Greece, Dr Stavros Kromidas wrote his chemistry dissertation 'The Development of new chiral phases in HPLC' supervised by Heinz Engelhardt, Professor of Instrumental Chemistry and Environment Testing, at Saarland University, Germany. Following a management job with Waters GmbH, in 1989 Kromidas founded Novia GmbH. Since 2001 he has been a consultant and author of specialist books on High-performance liquid chromatography (HPLC) and validation. He focuses on the comparison and selection of stationary phases and gradient optimisation, as well as the use of state-of-the-art HPLC and Ultra-high performance liquid chromatography (UHPLC).

**Time and money play crucial roles in obtaining results in analytics. How would you rate the significance of these two factors?'**

'Just like in real life these two factors are interdependent: The more time – which is ultimately money – you invest, for example by using different ionisation techniques, the more reliable the results and their interpretation. There are always quick and cheap ways to find what you're looking for, but you don't always know how reliable the results are.'

\* 'The Gradient in HPLC for Practitioners' by Stavros Kromidas, is due to be released soon by Wiley.



Tarush Kothari MD is a Physician Informaticist with Northwell Health Laboratories in New York and Assistant Professor in Pathology and Laboratory Medicine at the Donald and Barbara Zucker School of Medicine. He is a board-certified anatomical and clinical pathologist in New Hyde Park, New York, and is affiliated with multiple hospitals of the Northwell Health System. He received his medical degree from Mumbai University, India, and pathology and laboratory medicine training at Northwell Health in New York. He gained a Master's in Public Health from Columbia University, New York, and is also board-certified in the sub-specialty of Clinical Informatics.

There was clear value to the laboratory data in providing clinical decision support based on evidence-based criteria, reducing variability and latency in diagnosis and preventing disease progression, as well as improving clinical documentation of disease severity, he said. In addition to delivering a better clinical outcome for patients, Kothari added, the data offered a better understanding of the risk of disease in the population and reduced in-patient costs for severe acute kidney injury and CKD. MN

## Solid IT hardware and communication

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

industrial mobile handheld computers, smart panels, smart touch computers, industrial & panel PCs, medical PCs & display.

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

'Adlink products also support multiple operating systems and

include comprehensive and easy-to-use software packages and services,' the manufacturer confirms.

### Medical panel computers

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

'The MLC 5 medical panel computer is designed for digitally integrated operating theatres to enable easy access to PACS images, EHRS and other relevant patient data.

'The device allows surgeons to manage the patient's vital parameters and other critical information during surgery', the Taiwan company explains. 'The MLC 5 therefore is ideally used to simplify surgical patient data monitoring with superior graphic processing capabilities.'



The 70th Annual Meeting of the German Society for Hygiene and Microbiology

# No all clear for nosocomial infections

Report: Brigitte Dinkloh

Experts at the 70th Annual Meeting of the German Society for Hygiene and Microbiology, held in Bochum, Germany, exchanged information on newly discovered resistances. 'Specifically, resistance against a class of antibiotics that has, so far, always been viewed as a reserve appears to be developing more intensively than previously assumed,' explained Professor Sören Gatermann, congress president and head of the Department for Microbiology at Ruhr University Bochum. The cause of resistance are different enzymes which make the antibiotic ineffective; its identification needs the most up-to-date molecular procedures, to determine which medication will be effective for a certain patient.

There is another class of resistances causing concern among scientists. Mutations in the bacterium itself lead to certain antibiotics becoming ineffective. These resistance mechanisms, which were neither acquired nor depend on inactivating enzymes, are occurring increasingly. The European Committee on Antimicrobial Susceptibility Testing (EUCAST) determines the limits up to which a bacterium is still considered treatable with antibiotics. New resistances are often hard to detect, Gatermann explained, 'so we must work on a genetic level to determine which treatments are likely to be effective for a patient.'

## Cause of resistances and regional variations

Therapy with antibiotics is the only



The congress presidents agreed that comprehensive MRSA screening of hospital admissions wastes resources

treatment to affect not only the patient treated but also all other patients. If an antibiotic is used in the intensive care unit (ICU) this not only affects the bacteria of the treated patient but also the entire hospital and its environment. This leads to different resistance profiles that can vary significantly from country to country. However, in-patient facilities account for a relatively low proportion (10-20%) of the overall daily doses of antibiotics administered. Antibiotics are far more commonly prescribed in out-patient care. There are also big regional differences: In the East of Germany the prescription rate is low, with the highest daily doses being prescribed in the Saarland, although this represents only half of the prescriptions in France.

'Each patient enters hospital with between two to three kg of bacteria. Up to 10% of the population already carry multi-resistant pathogens on admission,' explained Professor

Frauke Mattner, congress president and Head of the Institute for Hygiene at the Cologne Municipal Hospitals Group. The origin of the pathogens is still unclear. It is likely that they do not originate in drinking water but are spread through food, foreign travel or intensive animal farming. A certain proportion may also be spread from patient to patient in medical facilities. Which of these causes represents which proportion of the colonisation should be the subject of research to help tackle the problem in the future.

## Comprehensive screening is not helpful

The congress presidents agreed that comprehensive screening of patients for MRSA and multi-resistant gram-negative bacteria on admission is a waste of financial and staffing resources as well as counter-productive. Although patients in more frequent contact with hospitals and care facilities are at higher risk of

colonisation with MRSA, pure MRSA screening would take no account of other pathogens. Each individual hospital should determine which risk groups typically prevail in their facility and should then decide which type of screening and procedures are likely to be effective. This approach corresponds with the evidence-based recommendations from the Robert-Koch Institute (KRINKO).

Gatermann explained that higher staff levels and adherence to hygiene regulations are more effective than screening all patients, particularly for multi-resistant gram-negative bacteria. Also, the diagnostic sensitivity for gram-negative pathogens is not particularly high, with patients sometimes having to be examined over and over again.

General screening could lead to say 400 patients declared as being colonised when, in reality, only one is, Gatermann explained. A screening requirement would therefore lead to inadequate care for 399 patients. It would be better to carry out specific screening based on the epidemiology and risk group for whom the most benefit can be expected. 'Wrong determination of resistance can also have severe consequences in the case of MRSA, as the patient is not given the correct antibiotic. The probability is 1:1. This means that every other patient may receive incorrect treatment.'

## More university education and academisation of care

Hospital hygiene has experienced staff shortages in Germany for years. Around 1,000 specialists for hospital

hygiene are required. However, universities are not being encouraged, and Chair of Hygiene positions are only filled with delays or not at all. Only 7 out of 35 medical faculties have a department chair of hygiene and epidemiology. However, there has been considerable improvement over the last few years in the recruitment of hospital hygiene profes-



After receiving his doctorate, Professor Sören Gatermann began his career as a research associate at the Institutes for Microbiology at universities of Hamburg and Lübeck in Germany. His habilitation in Medical Microbiology was completed in 1991 and he received the Venia Legendi and specialist accreditation in 1992. Two years later he was awarded a C3 professorship at Mainz University. The professor has been Chair of Medical Microbiology at the Ruhr University Bochum since October 1997. From 2009 he has also headed the National Reference Laboratory for Multidrug-resistant Gram-negative Bacteria, and became head of the National Antimicrobial Susceptibility Testing Committees (NAK), the German branch of EUCAST, in 2014.

Developing new substances beyond commercial interests

# Support from the other end of the world

Partners who could hardly be further apart – yet have a lot in common – have united to fight resistant pathogens. The International Consortium for Anti-Infective Research (iCAIR) was founded last January. Hanover Medical School (MHH) and the Fraunhofer-Institute for Toxicology and Experimental Medicine (ITEM) are participants in Germany. The third partner, the Institute for Glycomics (IfG) at Griffith University, Gold Coast, Australia, is nearly 16,000 km away as the crow flies. That enormous distance has not stopped the German-Australian research cooperation from achieving its objectives: the development of new agents against infections. Professor Armin Braun, Head of Preclinical Pharmacology and In Vitro Toxicology at Fraunhofer ITEM, explains the specific potential of this long-distance alliance.

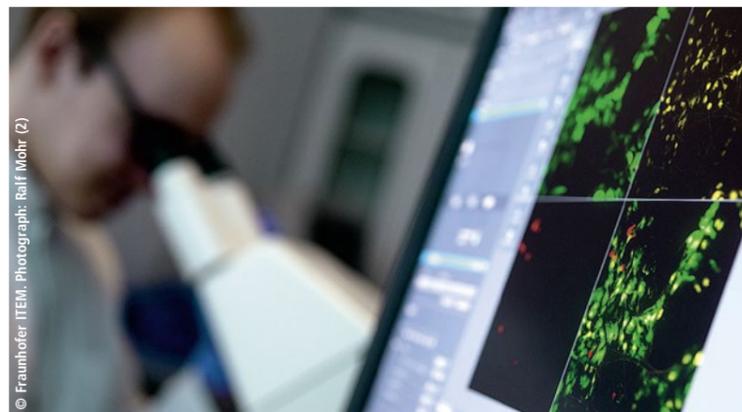
Report: Wolfgang Behrends

The idea behind iCAIR is simple. The partners combine their respective strengths to create a project that's more than the sum of its parts. IfG Director Professor Mark von Itzstein contributes considerable expertise in the development, design and optimisation of substances; he was a major driver behind the development of Relenza, a highly effective flu medication. 'However, what was missing from his side was the translational aspect relating to toxicology, quality assurance and preclinical proof-of-concept,' Braun explains. ITEM and MHH will contribute this know-how.

## Where pharmaceutical firms pull out, others step in

The partners are funding the project. Fraunhofer finances the iCAIR programme; MHH and IfG fund their own projects. This financial autonomy is central to the consortium, Braun explains.

'The pharmaceutical industry has now largely scaled down development of anti-infectives. However, iCAIR facilitates the development of



new substances beyond commercial interests. Research is to be refinanced via own patents.

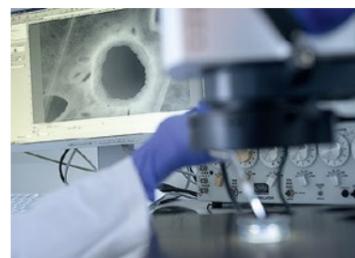
'Making do without the development of new anti-infectives, only because the pharmaceutical industry cannot find the right business model, is no alternative.'

Alternative sources of finance, such as the Gates Foundation, public funding from the BMBF (Federal Ministry of Education and Research) or the iCAIR alliance, are the way forward in this situation

Helped by 3-D confocal microscopy, scientists observe individual cells of the human lung structure. This also enables them to observe the reaction of different cells, e.g. immune cells, to a selected medication

## Different pathogens – similar methods

The need for new anti-infectives is substantial: Bacteria such as *Pseudomonas aeruginosa* and *Neisseria meningitidis*, the mould *Aspergillus fumigatus*, as well as influenza and para-influenza viruses are an international problem.



The activity of bronchial muscles (see monitor in background, with open bronchus) can be well observed. The bronchi dilate or expand according to the type of medication or substance administered

'Anyone, anywhere in the world, can become infected with influenza, and the changes in social structures are increasing the problem. People are living longer and are thus more prone to infections.' The growing number of immunosuppressed patients and those who have received organ transplants also offer pathogens new scope for attack. 'There are hardly any effective drugs against fungal infections in particular, which is why survival rates for outbreaks on the ICU are frequently very low.'

## A dizzying pace of drug development

iCAIR's biggest progress is in new agents to fight influenza. The preclinical proof-of-concept stage has been reached and the first drugs could be ready for clinical use in 2-3 years. By pharmaceutical standards, where

development cycles can be 15 years or longer, this constitutes an almost dizzying pace. 'Although this does not apply to all substances,' the professor points out, 'we can usually shave off around 1-3 years.' This optimisation is achieved through clever division of labour: MHH and IfG concentrate on the identification of possible drug targets. The Australian partner selects and generates the substances from which new pharmaceuticals are to be developed. The subsequent preclinical phase is in the realm of Fraunhofer ITEM, which will also support the further clinical development and production of the substance.

Although the partners are at opposite ends of the world, the cooperation works well, Braun says. 'The fact that all those involved are professionals – some with decades of experience in their area of expertise – makes the cooperation really enjoyable.'

The new iCAIR consortium is already receiving good feedback from experts; several research institutions worldwide have expressed interest in participation. In the long term, this additional expertise and resources should help to develop a global network for the joint development of anti-infectives.

The current leading topic at iCAIR is new substances against influenza: 'Germany as well as Australia recently had huge problems with 'flu epidemics because vaccines are not effective,' Braun says. Meanwhile, although there has been a paradigm shift that



After gaining her medical degree, **Professor Frauke Mattner MD** trained in Laboratory Medicine in Hamburg, Germany, and then specialised in Hygiene and Environmental Medicine at Hanover Medical School (MHH), with habilitation completed in 2007. In that year she also became head of the Hygiene Department at the Institute for Medical Microbiology and Hygiene, Lübeck University Hospital. Since 2010, the professor has headed the Institute for Hygiene at the Cologne Municipal Hospitals Group, University Hospital Witten-Herdecke, Campus Cologne Merheim, and was appointed adjunct professor at the MHH in 2012.

sionals. In North Rhine-Westphalia for instance the coverage is now at 90% of the KRINKO capacity recommendation. But Frauke Mattner sees a need for action by international comparison: 'Germany brings up the rear in the ratio between nursing staff per patient, and we have the least academic staff. But it has been proven that an increase in the number of nursing staff with academic qualifications can reduce the number of nosocomial infections by 20-30%. 'This was evaluated across Europe in the 2014 RN4Cast Study. The newly designed nursing training programmes neglect academisation. They have increased quantity at the cost of quality, but both are required.'



**Dr Armin Braun** is head of Preclinical Pharmacology and In Vitro Toxicology at the Fraunhofer-Institute for Toxicology and Experimental Medicine ITEM, in Hanover, Germany, and professor of Immunology of the Respiratory Tract at Hanover Medical School (MHH). A member of the German Centre for Lung Research (DZL), his research focuses on the preclinical development of substances against respiratory diseases. He uses innovative processes such as live tissue slices (precision-cut lung slices; PCLS). Braun has co-authored more than 150 scientific articles in international scientific publications.

promises improvements, 'we are no longer fighting the pathogens directly but are working on the viruses entry ports into cells. Researchers test their agents on human tissue taken from tissue slices, such as healthy parts of tissue obtained during tumour resection. This is a completely new approach for us,' Braun notes. The tissue sample is infected with viruses and kept alive for several weeks to observe interactions between tissue and pathogen.

'This is a model which comes very close to the actual reaction occurring in the human body.'

Examining the link between social media and STIs

# A rise in sexually-transmitted infections

With the ever-continuing growth of social media, experts fear there may be a link between online forums and an increase in sexually-transmitted infections, **Mark Nicholls** reports

While specific data remains limited on a possible connection between online forums and sexually-transmitted infections (STIs), this has become an area of increased focus. The subject was, for example, aired in April by one of the UK's leading experts in the field, during the 28th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), in Madrid. At the four-day event, Dr Gary Whitlock, from the Chelsea and Westminster NHS Foundation Trust, delivered a presentation on social media and its impact on STIs.

Speaking to European Hospital, he explained that STIs have risen over the past 10 years.

'At the same time, social media use has also increased,' he said. 'For dating, there has been a change in the use of social networking methods, most recently with Geospatial Networking (GSN) app use. Other changes in sexual mores – changes in socially acceptable sexual behaviour – have also occurred.'

'There is an association between increased social media use and increase in some STIs. However, it is not clear if this is a causal relationship.'

Whitlock, a consultant physician in sexual health and HIV medicine at Chelsea and Westminster Hospital's 56 Dean Street clinic,

described the history of social media, social networking and geospatial networking (GSN) apps both in the general population and MSM (men who have sex with men).

### Using social media to promote health education

The prevalence of social media use for finding sexual partners has reached new heights nowadays, yet social media could also have a positive impact, as Whitlock pointed out in his conference presentation. There are ways in which social

Social media use to find sexual partners has become a common practice in Europe



media can be used to promote sexual health and help decrease STIs. 'There are opportunities to harness social media apps (and social media in general),' he said, 'to better educate users including education about STIs and health promotion.'

He then highlighted examples of social media use in educating users, such as the IwantPrEPnow website and 56 Dean Street's own 'Dean Street Prime' web-based tool.

iwantPrEPnow.co.uk was created mostly by volunteers to raise awareness of and access to PrEP – Pre-Exposure Prophylaxis – a new HIV prevention approach where HIV-negative individuals use anti-HIV medications to reduce their risk of becoming infected. It informs in easily understandable terms and short videos about the possibilities of the



**Gary Whitlock MD** is a consultant physician in sexual health and HIV medicine at Chelsea and Westminster Hospital's 56 Dean Street clinic, Great Britain. With a clinical interest in gay men's sexual health, he is lead for high-resolution anoscopy and, at Dean Street, the CODE clinic. His research interests include pre-exposure prophylaxis (PrEP) and the impact of rapid testing for STIs.

approach, who might need it and how best to use the medication.

The Dean Street Prime tool is a members-only online service for users of the HIV and sexual health NHS clinic in London offering a benefits package. Users can choose between five different programmes and will receive text messages with details of exclusive services, events and information promoting a healthy sexual behavior and relevant lifestyle changes in order to help them stay HIV negative.

These examples are just a few initiatives created to promote STI knowledge. There is a broad audience to be reached, Whitlock explains. In terms of social media in relation to sexually transmitted infections, the target audience is 'sexually-active people', the specialist points out, although he concedes that, at this stage, what specific benefits interventions may have are not yet clear.

The European Congress of Clinical Microbiology and Infectious Diseases

# Common sense defeats infection outbreaks

Report: **Lisa Chamoff**

**Loreen Herwaldt** doesn't believe there is a 'gold standard' for infection prevention, but she knows there are common sense steps that hospitals can take to prevent disease outbreaks.

'I don't think there's a gold standard, or a silver bullet, but more like standard operating procedures,' says Herwaldt, an infectious disease specialist at the University of Iowa, USA. 'These are things that make sense and have been developed over time.'

Herwaldt discussed the standard of care for infection control during the session 'Hands-on infection control – what does actually work to prevent infections?' at the European Congress of Clinical Microbiology and Infectious Diseases in April.

### Engineered control and sensible renovation

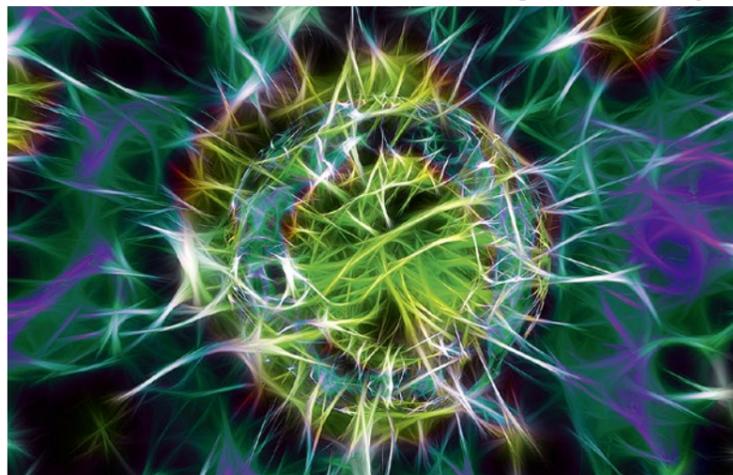
Herwaldt's 'infection control hierarchy' includes personal protective equipment for hospital workers and screening checklists for patient, such as asking about travel in cases of Ebola.

Hospitals can also use what Herwaldt calls 'engineered control', such as placing UV lights in air ducts, installing appropriate ventila-

tion in isolation rooms and disinfecting drinking water systems and cooling towers to prevent the spread of legionella.

Hospital executives should also consider infection control when planning renovation projects. 'During the SARS epidemic, in Toronto, the hospital hit hardest had renovated its emergency department and decided it was too expensive to put in private rooms,' Herwaldt notes. 'There were curtains. A number of patients became ill because

Borrowing technologies from other disciplines could help outbreak investigations



they happened to be in the ED at the same time.'

### Thinking outside the box

The specialist also discussed evolving technologies that have been borrowed from other disciplines to investigate outbreaks. For example, partial or whole genome sequencing and statistical modelling has emerged as a way to pinpoint the source of certain outbreaks. 'It's probably not going to be an everyday tool for most hospitals, but it could be useful in some cases,' Herwaldt believes. Regional modelling of carbapenem-resistant bacteria, for example, shows the highest



**Dr Loreen Herwaldt** is an infectious disease specialist at the University of Iowa, USA, where she researches healthcare-related infections and infection prevention protocols. She holds a medical degree from University of Wisconsin School of Medicine and Public Health.

incidence are in short-stay hospitals and, she notes, larger referring hospitals have a lower prevalence.

'Even modelling on a community level can help inform investigations at individual hospitals,' she says. 'If there are facilities that are the most problematic, you need to screen patients from those facilities.'

Facilities can also use human-factors engineering to inform infection control protocols. In her presentation, Herwaldt explained how technology, such as cameras in patient rooms and markers on personal protective equipment, could be used to analyse hand hygiene in hospitals.

'Many of the things I'm talking about can play a role in day-to-day infection prevention,' the expert points out. 'We've been able to move forward because we've been interacting with people in other disciplines.'

*'A true shift in oncology'*

# Immunotherapy advances

Report: Mélanie Rouger

**Bigger lesions, better outcomes** - With immunotherapy, CT may show bigger lesions, which doesn't necessarily mean the disease is progressing. As treatment works, it can cause 'pseudo disease progression' - just one of the many revolutions immunotherapy triggers in cancer imaging, expert Professor Clarisse Dromain explained during ECR 2018. A range of new immunotherapy approaches in recent years include non-specific immune-stimulant, adoptive T-cell therapy and immune checkpoint inhibitors (anti CTLA-4, anti PD1 and anti PDL1). The immune checkpoint inhibitors (ICIs) - commonly used and intensively studied - profoundly impact on cancer treatment, she explained. 'Their mechanism of action signifies a true shift in oncology. Instead of targeting tumour cells, ICIs target the immune system to break cancer tolerance and stimulate anti-tumour immune response.' These new (2011) drugs for melanoma, lung, bladder, renal, and head and neck cancer, have shown a remarkable and long-lasting treatment response.

ICIs trigger immune and T-cell activation, producing unusual response patterns. 'First we observe delayed response - a lot of stable disease with very slow, steady decline in total tumour volume; this is really a long duration response.' If immunotherapy stops, the response duration without progression is very long. 'This is really specific to immunotherapy.'

## Dealing with pseudo-progression

Imaging has revealed new responses, e.g. flare phenomenon and response after initial increase in tumour border and initial appearance of new lesions. 'These new responses are called pseudo-progression, and could be due either to tumour site infiltration by immune cells or continued tumour growth until a sufficient response develops due to the time required to mount an adaptive immune response,' Dromain explained.

Recent research suggests that pseudo progression with anti PD-L1 may appear in about 5% of patients. An increase of tumour burden during immune checkpoint blockade (ICB) treatment is more likely to reflect true progression than pseudo-progression, Dromain said.

'We talk a lot about pseudo-progression, but true progression is more common.'

The immune system may be more reactive in a younger population and pseudo-progression could be associated with a clinical worsening, especially in lung cancer. Pseudo-progression may occur any time, but mostly appears around 12 weeks after therapy onset, especially in melanoma. Additionally, pseudo-progression may concern all organs, but most commonly lymph nodes, lung and liver.

After three types of chemotherapy, a patient with colic cancer MSI positive - a very nice indication for immunotherapy - showed progres-

sion. 'We did a clinical trial and tested an anti PD-L1 for liver metastasis. A few months after treatment onset, we saw very good response in the liver of this peritoneal lymph node,' she said.

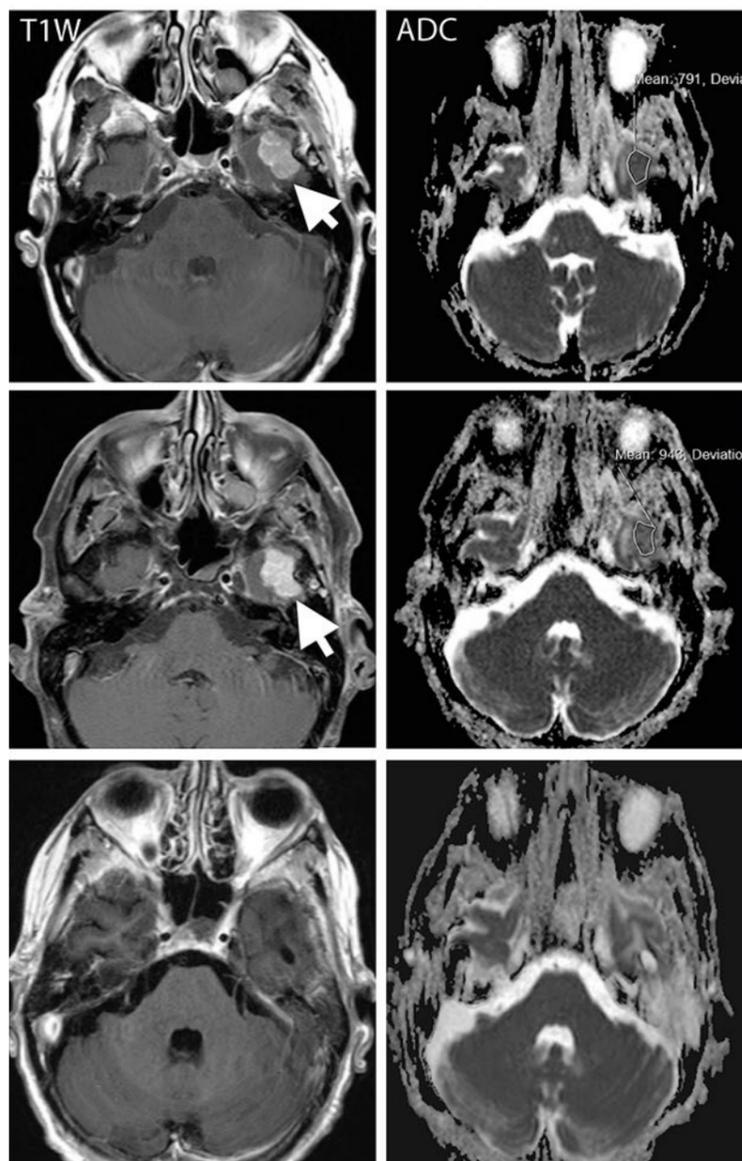
'We suggested the possibility of flare phenomenon and performed cytology by lymph node aspiration. This showed mature lymphocyte, so we continued the treatment and the liver response was very good. The lymph node disappeared.'

## Updating guidelines for new responses

New criteria have been developed to help manage the new responses. To overcome the limitation of RECIST criteria to assess these specific changes in tumour burden, so-called irRC criteria were established, on the basis of WHO criteria (bi-dimensional measurements, end target lesion + five cutaneous targets).

'This was designed for melanoma. The main difference from classical WHO criteria is the inclusion of measurements of new target lesions into disease assessments and the need of a four-week CT reassessment to confirm progression,' Dromain explained.

**Male with metastatic melanoma commencing on immunotherapy drugs nivolumab and ipilimumab.** Pre-treatment (top) contrast-enhanced T1-weighted image shows enhancing metastasis in left temporal lobe (arrow), associated with low ADC value (791 x 10<sup>-6</sup> mm<sup>2</sup>/s). Treated for eight weeks, the lesion shows minimal change on the T1-weighted image (arrow) but demonstrates 20% increase in the ADC value (948 x 10<sup>-6</sup> mm<sup>2</sup>/s). 16 weeks after treatment (bottom row), the lesion has regressed, showing no appreciable enhancement on the T1-weighted image, although residual post-treatment high ADC value cystic area is visible



**Dow-Mu Koh MD** is consultant radiologist in functional imaging and Professor for functional cancer imaging at the UK's Royal Marsden Hospital and its academic partner The Institute of Cancer Research (ICR). His research focuses on functional imaging techniques for tumour assessment.

Things did not turn out so well in clinical practice. 'It was a real nightmare to have 15 target lesions, with two-dimensional measurements. So, the RECIST working group established i-RECIST (a new consensus guideline that recommends assessing lesions - target, non-target and new - separately) based on one-dimensional measurements and including the same choice of lesions,' she said.

Pseudo-progression should be considered until PD is confirmed, but scientific rationale is lacking



**Clarisse Dromain MD PhD**, head of the cancer imaging department at Gustave Roussy Cancer Campus University Hospital, Paris, researches interventional and diagnostic breast imaging. She is a member of the European Society of Radiology and several other international and national scientific organisations.

regarding a time window to do so, Dromain explained.

'Studies give different results. For example, Nishino et al observed 103 patients with melanoma, with 4% of pseudo-progression. Median time to peak tumour burden was 5.5 months, median time to the first scan showing tumour burden decrease, compared to the prior scan, was 6.8 months.

'All patients had two or more consecutive scans demonstrating PD over four-week time frame before response. Recently the RANO working group on neuro-oncology recommended a three-month period for PD confirmation.'

## Immunotherapy follow-up with MRI

Today, immunotherapy is notable in imaging, but follow-up with CT is not assured in the peripheral limbs, brain and bone marrow, whereas MRI offers specific benefits and, combined with PET, may bring even more results. Research is needed on quantitative techniques and tracers developed to fully exploit that potential, Professor Dow-Mu Koh (Sutton/UK) believes.

Imaging assesses treatment response, predicts response and patient benefit, identifies complications, offers disease prognosis and evaluates relapse, Koh said, adding: 'We are quite far from achieving these objectives.'

MRI techniques provide morphological and functional imaging - and the potential for hybrid imaging. Research continues on using soft tissue contrast of MRI to enhance disease assessment, especially in disease sites that are poorly visualised with CT.

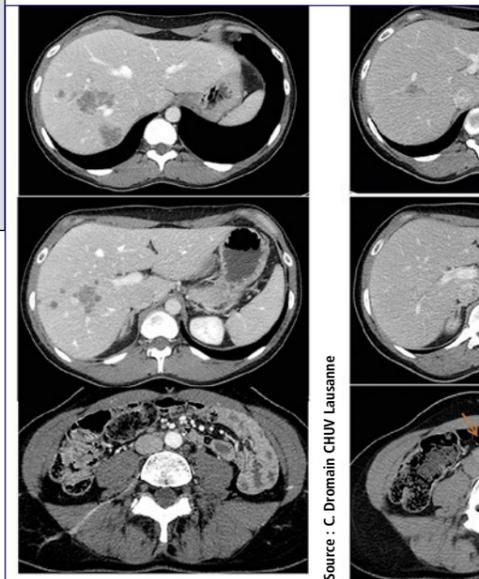
Koh: 'MRI is useful in areas not naturally included by CT studies, for instance peripheral limb. Small brain metastases can challenge CT, as can disease confined to bone marrow.' Current iRecist criteria enables identification and documentation of responses not typically observed in traditional systemic treatment. The new (2017) guideline enables classification of assessments after i-unconfirmed progressive disease (iUPD) has occurred - with following disease progression confirmation in 4-8 weeks.

## Spotlight on flare reaction

Radiologists must beware of challenges inherent in follow-up imaging within that time. 'What we're observing at eight weeks is pseudo-progression or the so-called flare reaction,' Koh explained. The situation that needs MRI imaging is usually more complex than for CT. 'Lesions can grow,' he added. 'In our research we noted a decrease after 16 weeks, and after 24 weeks the lesion was totally gone.'

Radiologists must also recognise and visualise immune related events: one MRI strength is to seek the presence of hypophysitis, Koh noted.

'We know that this has higher incidence with CTLA-4 blockade; it has a reported incidence of 17%, and may be associated with pituitary failure associated with low ACTH and TSH levels.' A patient often experiences fatigue and headaches.



July 2015 BL

December

Source: C. Dromain CHUV Lausanne

*Radiation garment lowers exposure*

## Zero-Gravity radiation protection

In today's operating rooms, increasing fluoroscopic procedures keep interventionalists at work longer, wearing the hugely heavy lead aprons necessary for protection against radiation. Chronic back pain is often accepted as something that simply comes with the job. Relief has arrived at last in the form of Zero-Gravity, a suspended radiation protection system designed to increase radiation protection whilst also eliminating the weight burden for the operator.

With his team, Dr Andreas H Mahnken, Director of the Diagnostic and Interventional Radiology Clinic at Marburg University Hospital, Germany, found significant differences when comparing the suspended Zero-Gravity system to several conventional ones.

Asked about the link between wearing lead aprons and chronic back pain, Dr Andreas Mahnken pointed out that several survey-based studies in English-speaking countries, such as the USA and UK, have focused on cardiology departments. 'Around half of all respondents working in interventional cardiology said they've had back pain from wearing lead aprons. Thirty-five percent of these complaints are lumbar spine-related, 25 percent concern the cervical spine, and we see knee and hip complaints in 20 percent of cases.'

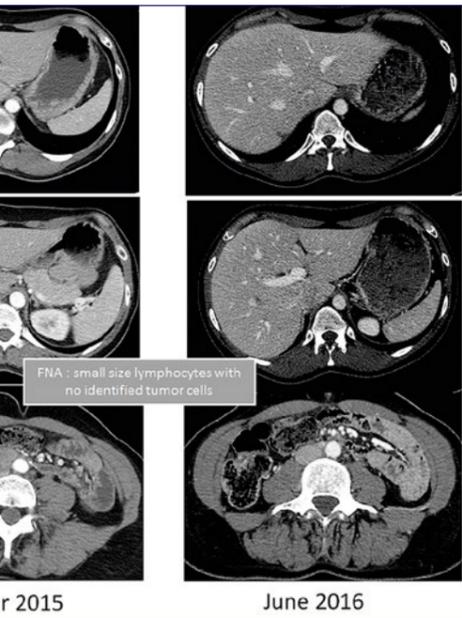
'Orthopaedic problems happen much more often than cataracts or haematological diseases, but they haven't been studied much, so far.'

At last year's ECR Mahnken presented results of his own study, which compared the orthopaedic burden of various radiation protection systems. What did he discover?

'We found clear differences between the radiation protection systems when it comes to physical strain on the user. The Zero-Gravity system reduced shoulder strain by about 80 percent.'

Brain MRI is currently best to observe pituitary gland changes. 'You look for symmetrical diffuse pituitary enlargement and thickened non-displaced pituitary stalk without any sellar erosions.' These changes need very early assessment, because established hypophysitis is irreversible, and means life-long hormone

**Pseudo progression on a CT examination in a patient with a metastatic colorectal cancer MSI+**



sure and lifts the weight burden

## 7 suspended protection



Dr Andreas Mahnken directs the Diagnostic and Interventional Radiology Clinic at Marburg University Hospital

Of his own experience with Zero-Gravity, he said: 'It's been liberating! It feels good to operate without all the weight. That's especially true for someone who has spent up to eight hours a day in the operating room over many years.'

'When using the Zero-Gravity system, I'm not as tired at the end of my working day as I used to be, and I'm definitely more relaxed.'

Does he thus believe Zero-Gravity should be used in every catheter lab?

'I would definitely support that,' he replied. 'Zero-Gravity isn't just an excellent radiation protection system. Its bigger potential lies in its ability to help alleviate orthopaedic stress on doctors.'

'First though, there needs to be more information on the orthopaedic risks of wearing conventional lead aprons. Physicians, hospital administrators and nurses still have limited knowledge and awareness of these problems. It would also be good for clinics to see Zero-Gravity as an investment in employee health, which current and future employees will appreciate.'

\* Zero-Gravity is distributed by Biotronik. Details: [www.biotronik.com/en-de/products/zero-gravity](http://www.biotronik.com/en-de/products/zero-gravity)

therapy. Another MRI benefit: MRI does not utilise ionising radiation, so can be repeated in follow-up.

### MRI shortcomings

However, MRI has limitations, including the absence of confirmed prediction prognostic MRI biomarkers for immunotherapy. 'The search is on for what could help predict who would benefit from this treatment,' Koh said. Despite increasing studies, predicting if one is dealing with either pseudo-progression, hyper-progression or concealed response on MRI remains hard.

The overall rate of pseudo-progression is under 10%, and this

process could be due to infiltration of the tumour site by immune cells or continued tumour growth until a sufficient response develops. In hyper-progression, radiologists usually can observe accelerated tumour growth during treatment. HP is also associated with poorer survival, Koh said. Another key limitation for morphological MRI is not spotting changes in the lungs. 'Changes such as pneumonitis will always be better appreciated on CT,' he added.

### Techniques to increase information output

Could radiologists use other views of MRI techniques to gain better

functional information? 'MRI techniques result in quantitative measurements, which reflect different aspects of disease pathophysiology. We have DWI, CE MRI... and we also have magnetisation transfer MRI, which is very interesting to assess immunotherapy,' Koh said.

Magnetisation transfer MRI is the process by which macromolecules and their associated water molecules cross-relax with protons in the free water pool. Their interaction can be measured by applying radio frequency to the pool, using the off-resonance MR pulse.

All these techniques are in research to increase contrast between tissues.

Hybrid imaging could also help tremendously, but PDG PET may show false positive result at follow-up due to flare response. Therefore, novel tracers are being explored, namely N-(2-(diethylamino)-ethyl)-4-18F-fluorobenzamide (18F-FBZA), 64CU-Radiolabeled HAC-PD1, 64CU-Radiolabeled DOTA-CTLA4, and 68Ga-NOTA-GZP.

'The idea is to develop PET imaging tracers that can identify and predict treatment response, which can be explored alongside multi-parametric MRI measurements on a MRI/PET hybrid system as imaging biomarkers,' Koh said. How long this will take remains uncertain. ■



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Finding the right algorithms to tackle big data

# AI and machine learning

In conversation with Daniela Zimmermann, Executive Director of European Hospital, Tracy Accardi, Hologic's Vice President (Global R&D), spoke of the importance of innovation, tomosynthesis, artificial intelligence/deep learning and open dialogue with the radiology community.

Hologic addresses a broad spectrum of gynaecological, perinatal, aesthetic, skeletal and breast women's health issues. To enhance this approach, Tracy Accardi, of Hologic, explained the importance of working closely with radiologists.

'We are seeing the benefits of the significant level of investment we have been making over the last several years in bringing new products to the market. Within that, everything we do is around improving workflow for the radiologist and the technologist – and improving the experience for the patient.'

'When you think about tomosynthesis, for example, everybody raises concern about the time it takes to read an image. We constantly work on image quality and continue to develop a detection process that takes in more information from a pixel perspective, but does not increase the time it takes to do the scan or read the image. This turns out to be a win for both the patient and the radiologist.'

'When we talk about a focus on workflow improvements, we need to get smarter with how to help radiologists so they are comfortable that they have looked at everything they need to look at with tomosynthesis and are not overwhelmed by the

amount of data. We have more than three years invested into looking at how to use deep learning to read the tomosynthesis data and direct radiologists to the things that they should be most concerned about.'

**How could deep learning, artificial intelligence and big data work?**

'We make continuous investments to ensure we have broad mammography data sets representing full variations of density and diagnostic outcome. To make deep learning really work, the more data you have, the smarter your algorithms are, so we're very focused on case collection. We know we will need thousands of known cancers with pathologically confirmed outcomes so that we can teach the algorithm how to find those occurrences in the data.'

'We have developed the ability to grade how well our algorithms are working. I think our competitive edge is that we have developed a lot of knowledge over time about how to interpret mammography images, and have invested in learning how radiologists think and what they need to do deliver the best standard of care. We know that we need to look at all the ways that breast

cancer presents itself. We want our algorithms to tell the difference between a mass that the radiologist should worry about and one that can be dismissed.'

**Other than wait and see, how do you safely distinguish slow growing masses?**

'There are indications of a fast growing or aggressive cancer, for example the presence of spiculations or unusual vascularization in the image. If a mass is perfectly round and smooth walled it is most likely non-malignant and you can train your algorithms to know the difference. The more three-dimensional your data is – and tomosynthesis is a perfect example – the better your algorithm can be. The radiologist needs to be able to focus on the observations where the algorithm cannot be positive.'

**Might deep learning replace the radiologist?**

'From a deep learning perspective, the space was held back for a long time given available tools and limited processing capability. Developments over the last several years have delivered significant improvement at reasonable cost in both areas. I believe we'll see significant industry investment in delivering the promise of deep learning to the radiologist, and I'm very excited about that.'

'What I'm fascinated about is that, with deep learning, you have to make very sure you are asking the

algorithm the right questions, otherwise you don't get the right answers. It sounds very simple, but you can otherwise fool yourself about what you think the algorithm is telling you. We have invested a lot of time speaking with radiologists around the world about how they want to see deep learning help them with questions that they want to try to answer.'

'Deep learning is not about replacing the radiologist, it's about making radiologists as efficient and positive as they can be about their diagnoses, and perhaps not having to look at 40-50% of the images that are not going to be a problem. Giving the radiologists the ability to confidently focus on just the cases that are flagged with issues is the primary goal.'

**Do you see more adopters, or will process be slow?**

'While capabilities of deep learning are being felt all around us in our daily lives – I anticipate that adoption in the interpretation of mammography will be relatively slow because the radiologist, quite rightly, needs to be extremely confident. At Hologic, we are completely committed to delivering solutions that gain that level of confidence.'

**What is the next step?**

'Our focus is on continuously amassing fully validated tomosynthesis images, consulting with radiologists and training our algorithms to estab-



In 2014 Tracy C. Accardi MSc (MEng) joined Hologic as Vice President of Global Research and Development at the Breast and Skeletal Health Division, where she leads a globally diverse team of 220 engineers and scientists, to develop systems for 2-D and 3-D mammography, breast diagnosis/biopsy, and bone densitometry. Prior to this appointment, she was Chief Technology Officer at OmniGuide Surgical for two years, leading development and marketing of advanced surgical energy solutions for minimally invasive surgery. Earlier roles include those at MedNest Consulting, Coviedien, Codman & Shurtleff (a division of Johnson & Johnson), Philips Healthcare and General Electric (GE). Among other commitments, Tracy Accardi is on the board of 'A Better Chance', a non-profit organisation in New York City committed to the education of academically talented, promising young women from under-served communities.

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'We will build toward our future with deep learning. I firmly believe that deep learning is critical to globally transform breast patient care through insight-driven, innovative solutions.'

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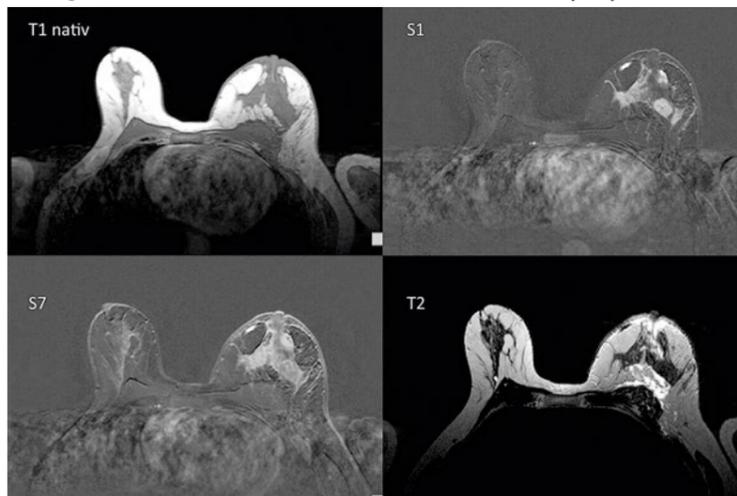


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Report: Michael Krassnitzer

'Breast cancer rates are continuously increasing, and we don't yet have a means of prevention,' said Dr Clemens Kaiser, from the Medical Faculty Mannheim, at Heidelberg University, who believes the only way to save more patients from death, after providing the best possible diagnostics procedures, is via precision medicine: the right treatment at the earliest possible time. The radiologist spoke of the implementation of precision medicine for breast cancer during a Siemens Healthineers satellite symposium held at the 2018 European Radiology Congress in Vienna.

Dynamic multiparametric breast MRI showing cancer in the left breast



**Strong prognostic tool**

In Kaiser's view, the key to precision medicine in breast cancer treatment is MRI: 'Breast MRI images deliver a lot of prognostic information,' he confirmed. Studies have shown that breast MRI data allows conclusions as to the risk of metastases. Other studies have shown a link between breast MRI data and chances of survival. 'Breast MRI is a strong, non-invasive prognostic tool,' Kaiser confirmed. The inner structure, or margin of the tumour, oedema, the hook sign (a tumour branch) or necrosis – all of these can contain important information that can be decisive for treatment.

The problem is that automatic quantification of all these factors and ability to derive prognoses from them is not yet possible. 'However, the prerequisites are there,' Kaiser emphasised. The amount of medical data available is escalating – keyword: big data. Whilst in 1980 it still took seven years for the entire volume of available medical data to double, this now takes only a year. It is esti-



Radiologist Clemens Kaiser MD BA is a Senior Consultant and Head of the Division for Multimodal Breast Diagnostics at the Institute for Clinical Radiology and Nuclear Medicine, University Hospital Mannheim, Germany. He held his International Business Administration (EMA) diploma and Bachelor of Arts in Marketing Management, before gaining a PhD in medicine at the Friedrich-Schiller University Jena. His dissertation was entitled 'Duct-obstruction-sign – duct ectasia for differential diagnosis of DCIS vs papilloma in breast MRI'.

mated that by 2020 it will only take 73 days. The capability of computers has also increased in line with the level required for these tasks – a modern mobile telephone is 32,000 times faster than the best computers available at the time of the moon landings.

**Data quantification**

'Radiomics' might be the solution. The word describes a combination of medical image processing and radiological research into the analysis of quantitative image characteristics in large, medical image databases. This is based on the idea of being able to make statistical statements about tissue characteristics, diagnoses and the course of diseases using radiological

Continued on page 15

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## Gadolinium deposit in the brain

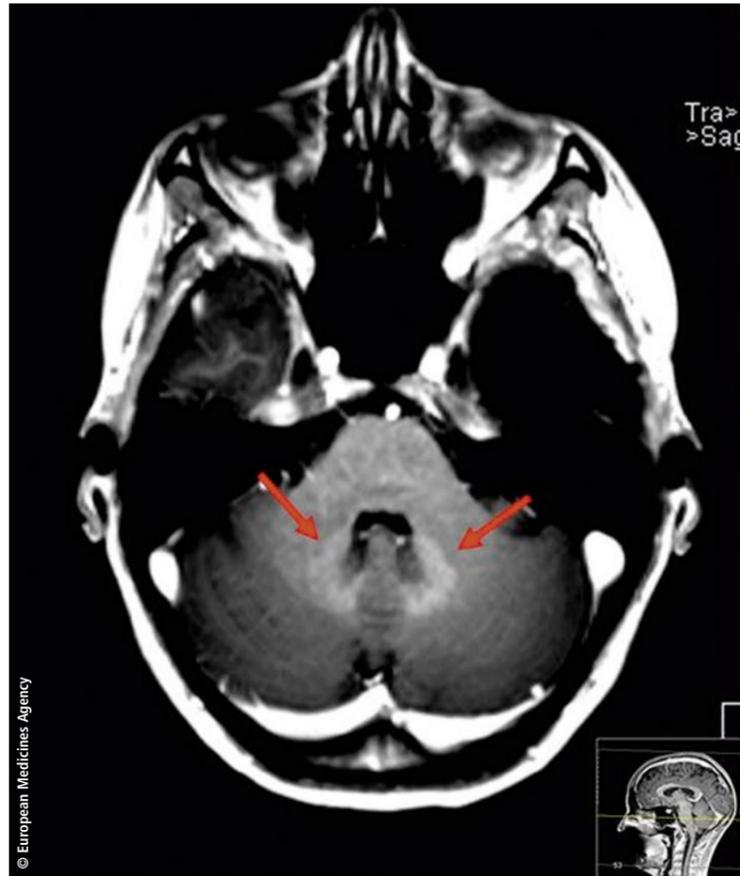
# A real threat or a phantom debate?

The European Medicines Agency (EMA) decided to suspend authorisation for certain linear gadolinium agents. The review by the Committee for Medicinal Products for Human Use (CHMP) states: 'There is currently no evidence that gadolinium deposition in the brain has caused any harm to patients; however EMA has recommended restrictions and suspensions for some intravenous linear agents in order to prevent any risks that could potentially be associated with gadolinium brain deposition.' Our EH correspondent spoke with Dr Alexander Radbruch, radiologist at the German Cancer Research Center in Heidelberg and at University Hospital Essen, who published several articles on gadolinium deposition in the brain.

Report: Sascha Keutel

**Dr Radbruch, would you explain the decision of EMA, to suspend the authorisation of four intravenous linear gadolinium based contrast agents for most of the indications in the EU?**

'Generally, a comprehensive risk benefit analysis has to be performed prior to the administration of every medication. For gadolinium based contrast agents (GBCAs) this risk-benefit analysis includes – among other factors such as diagnostic efficacy and the risk of further side effects – also the potential gadolinium deposition risk.



Contrast agent retention in the nucleus dentatus after 13 doses of a linear gadolinium-containing contrast agent since 2006 (Image courtesy of Professor Ernst Rummeny, Klinikum rechts der Isar, Munich Technical University).

Even though we do not know if any clinical correlates exist for the gadolinium deposition, the EMA decided that it is favorable to minimize the amount gadolinium in the body. Since numerous studies provided evidence that the total amount of gadolinium in

the brain can be reduced when macrocyclic GBCAs are used the EMA pursued a "precautionary approach" and concluded that the risk benefit ratio is no longer favourable for the linear GBCAs. Exceptions of this regulation are exclusively the use of gaobenate

or gadoxetic acid for liver imaging and gadopentetic acid for intraarticular joint imaging.

**Unlike the EU, the USA's regulatory body, Food and Drug Administration (FDA) currently does not see a need for action. Why are their opinions so different?**

'The FDA acknowledges that linear gadolinium based contrast agents deposit more gadolinium than macrocyclics. However, they come to a different conclusion within their risk benefit analysis and it seems that they will not remove any product from the market as long as no clinical correlates of gadolinium deposition are proven.'

**What is the current research status?**

'Animal experiments indicate that 24 hours post injection similar amounts of GBCAs – linear as well as macrocyclic – can be found, first in the cerebrospinal fluid and 24 hours later in the brain. However, four weeks after injection the total concentration of gadolinium in the brain is much higher with linear GBCAs than with macrocyclics – the latter being just slightly above the level of detection. Further animal experiments provided evidence to explain this finding: While the intact chelate is washed out over time for both – linear and macrocyclic GBCAs – the linear GBCAs partly dechelate and subsequently bind to different partners (eg macromolecules) which finally cause the hyperintensities seen on T1 weighted images. In macrocyclic GBCAs, however, no gadolinium release was detected. Consequently, the statement that all contrast agents deposit gadolinium is partly misleading. Gadolinium deposition is a process which has to be monitored over time: the intact chelate can temporarily be detected in the brain after both linear and macrocyclic GBCAs administration. However, dechelated gadolinium, which potentially stays in the brain, is found only after use of linear GBCAs.'



PD Dr Alexander Radbruch is a radiologist at the German Cancer Research Centre in Heidelberg and at the University Hospital Essen. He has published numerous papers on gadolinium retention and in 2015 showed, for the first time, that differences in gadolinium retention in the brain exist between macrocyclic and linear gadolinium-containing contrast agents. In 2017, the radiologist was chosen by colleagues in the category 'Radiological Research' as one of the world's 15 most influential people.

**Does the decision to restrict authorisation without proof of damage lead to unnecessary confusion among physicians? Do you understand this growing insecurity, even patient's fears?**

'In my opinion, the increasing uncertainty among physicians and patients as well as an unreasonable decline of GBCAs in clinically indicated situations is indeed the biggest threat in the current debate. Personally, I hope that the uncertainty will subside as time goes by. It's important to point out that the entire debate might be a phantom debate - an issue without substance.

'Generally, we need to explain our patients that GBCAs are an important component of clinical routine and often allow life-saving diagnoses. To date, GBCAs have been applied approximately 450 million times worldwide – 50 percent of these might have been linear and despite of this enormous number, no clinical correlates of the depositions are known, yet.

However, we should not forget that it also took us almost 10 years to disentangle the correlation between gadolinium and NSF. This experience with NSF might be one of the reasons why the EMA followed its precautionary approach.

**Are there potential alternatives to gadolinium-containing agents?**

'Currently, a lot of research on contrast-free MRI techniques is being conducted. At the German Cancer Research Centre we recently showed that sugar might potentially be used as contrast agent for brain tumour patients. Moreover, I'm sure, going toward diffusion-weighted imaging, which does not require contrast agents at all, will play a crucial role. However, I don't see any technique that, in the short run, might replace GBCAs.

**Could the debate lead to an overall ban?**

'I'm sure there won't be an overall ban. A ban would be absurd in view of the immense clinical benefit of GBCAs. I do hope that, in Europe, suspending the authorisation for linear GBCAs will calm the waves. Nobody can tell where the regulatory debate in the USA is heading. At the end of the day, I guess, markets will create facts. Look at paediatrics: Over the past two years, this field has witnessed a major shift in the USA and today 95 percent of GBCAs used are macrocyclic. Such developments might make regulatory decision superfluous.'



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Radiology and radiologists: a painful divorce

# The huge impact of AI

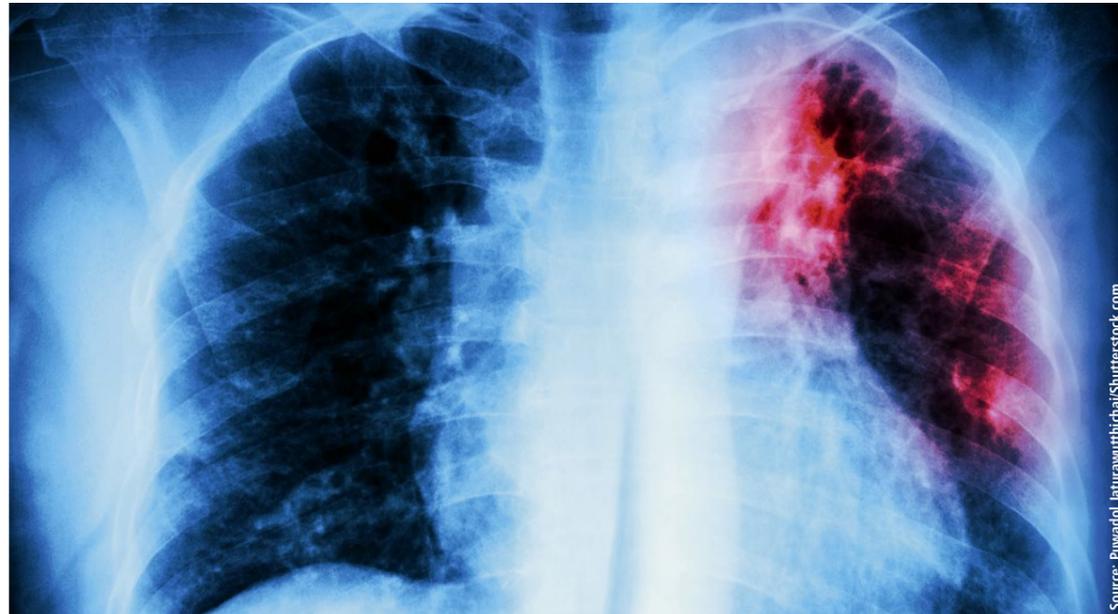
Artificial intelligence based applications will replace radiologists in some areas, the physicist Bram van Ginneken predicts. Michael Krassnitzer reports

'The profession of radiologist will change profoundly,' predicts Gram van Ginneken, Professor of Medical Image Analysis at Radboud University Medical Centre. The cause is automatic image analysis by computers (first published in a paper in 1963) and deep learning, the method with which a computer learns to analyse images not by features extracted by a radiologist, but directly from the images themselves. The title of his talk during the European Congress of Radiology (ECR 2018) in Vienna speaks volumes: 'Artificial intelligence and radiology: a perfect match. Radiology and radiologists: a painful divorce?'

For 50 years scientists had tried to build a system that could automatically analyse medical images. They failed. Humans are better. However, in 2013 they discovered that deep learning, an old idea from the 1970s, suddenly worked, thanks to better computers, more data to train on and improved algorithms to 'educate' artificial neural networks (the basis of deep learning). Currently, anything a human can do in one second, deep learning can also do. 'Take any classification or detection task for which a human expert looks at an image for one second, or scrolls through a scan (and prior scan) for a few seconds, and then knows the answers – that task can also be done by a computer using deep learning at, or above, the level of the human expert. It's still a lot of work to collect a well-annotated large data set and to engineer the deep learning system to perform well – but, it can be done.'

## AI-based applications

In Ginneken's view there are three types of applications: those replacing a radiologist's task, those helping the radiologist with a task, and those doing something a radiologist does not do today – and probably never will. The applica-



Source: Puvadol Jaturawuthichai/Shutterstock.com

A software Ginneken co-developed is designed to help (non-expert) readers detect tuberculosis in chest X-rays

tion BoneXpert automatically measures bone age from a child's hand X-ray, thereby replacing a human. 'This program delivers a precise and standardised reading, so that 50 percent of radiologists no longer look at the images', the Dutch physicist points out.

## Detecting TB in X-rays

Another application of this type, CAD4TB (Computer-Aided Detection for Tuberculosis) was co-developed by Ginneken. This is a software designed to help (non-expert) readers detect tuberculosis in chest X-rays. 'The first version was released in 2011 and immediately used in Zambia, even before it was approved,' Ginneken says. Meanwhile, CAD4TB is used in 24 other poor countries where radiologists are in short supply.

An example for an AI-based application assisting radiologists is Veolity, a lung screening workstation to read chest CT images efficiently. It includes automatic detection of nodules, automatic propagation of nodules found on prior scans, volumetric segmentation of solid, non-solid and part-solid nod-

ules, with a single click, automatic lobe assignment and nodule type assessment, emphysema scoring and coronary calcium scoring. 'With this software, radiologists are about 43 percent faster,' Ginneken explains.

An example of the third type of app is StratX, a cloud-based quantitative CT analysis service that supports endobronchial valve (EBV) patient selection and therapy choice by providing clinically validated information on emphysema destruction, fissure completeness and lobar volumes. This system enables assessment of all potentially suitable patients for that minimally-invasive treatment for severe emphysema. 'Radiologists have never done that,' Ginneken points out.

## Should physicians take over?

In terms of these automated services a question arises: Why involve a radiologist at all? Why don't the treating physicians take it on? Ginneken mentions optical coherence tomography (OCT), an ophthalmology imaging technique that gives a very detailed view of the retina. The technique was developed by ophthalmologists and is used exclusively by ophthalmologists; radiologists were never involved. 'I think this will be the case in any area of medi-

cine where new imaging modalities are introduced.' That situation does not sadden Ginneken. 'Don't think about radiology or jobs for radiolo-



**Bram van Ginneken PhD** is Professor of Medical Image Analysis at Radboud University Medical Centre and has co-chaired the Diagnostic Image Analysis Group since 2010. He also works for Fraunhofer Institute for Medical Image Computing (MEVIS) in Bremen, Germany, and is a founder of Thirona, a company that develops software and provides services for medical image analysis. Bram studied Physics at Eindhoven University of Technology and Utrecht University. In 2001, he gained his doctorate at the Image Sciences Institute on Computer-Aided Diagnosis in Chest Radiography, and he has (co-) authored close to 200 publications in leading international journals.

gists,' he says. 'Think about the positive impact AI intelligence will have on healthcare, globally.'

## Promising radiomics for breast MRI

Continued from page 12

imaging data, which could otherwise only be achieved through genomics or proteomics – i.e. exactly what Kaiser is envisaging with regards to breast MRI. 'We must,' he said, 'extract as much prognostic information from breast MRI images as possible.'

This is also not as easy as it sounds. The automated evaluation of image databases still faces obstacles. A very essential one is the lack of standardised data: 'Standardisation is the big challenge,' the radiologist emphasised. As long as the data is not standardised because each facility and institute carry out investigations in their own individual way, it cannot automatically be combed through for information. 'We must quantify the data,' Kaiser stressed. How might that be achieved? Kaiser envisions a

simple, solid decision tree, such as the one published by radiologists at the Medical University of Vienna around four years ago to differentiate between benign and malignant lesions in breast MRI. 'This tool has a proven accuracy of 88% for the distinction between benign and malignant tumours and helps to achieve a definitive diagnosis for a third of all lesions.'

If examinations were always carried out based on these decision trees this would result not only in a consistently improved precision and standardisation of a diagnosis but also in quantified examination data. 'This,' he believes, 'would be an opportunity to obtain comparable and valid data that could deliver prognostic information via radiomics.'

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*Unilateral higher education is the way forward*

# Swiss radiographers face many challenges

The radiographer in Switzerland faces many issues, from having the right education to positioning themselves both professionally and legally in the healthcare continuum. Before a large audience at ECR 2018, Yves Jaermann, head of the radiographers service Riviera-Chablais Hospital in Vaud Valay, reviewed the situation in his country



**Yves Jaermann** has headed the radiographers' service at Riviera-Chablais Hospital in Vaud Valay, Switzerland, since 1993. Before joining the Riviera-Chablais Hospital, he spent two years in Algiers, at the Issad Hassani University Hospital as radiographer and radiology teacher.

Report: Mélanie Rouger

The profession of radiographer was born in 1896, when the first X-ray machines were installed in hospitals. In Switzerland, radiographers began to organise themselves soon after. A professional association was founded in 1946. 'This shows our forefathers realised how important it would be to promote and defend their activity as a profession,' Jaermann pointed out.

Yet, according to him, the old idea of radiographers being the radiologists' helpers still haunts common memory. 'It's still present in the mind of some radiologists and radiographers, who are ashamed. Fortunately younger generations have a vision of complementary professional roles,' he said.

## A bachelor degree adds value

Among reasons for this sticky belief is that the education of Swiss radiographers remains unequal throughout the country. The bachelor's level was introduced in the French-speaking zone of Switzerland in 2002. However, in the rest of the country, radiographers can only take a diploma of higher education, which undoubtedly has less value, Jaermann explained. 'The professional skills of both diplomas are considered equivalent, but here I have to insist on the added value of the bachelor level. Students are made aware of research; their bachelor thesis is a first approach to this field. These young professionals have a slightly different professional behaviour, and position themselves more clearly in a partnership with other professionals, such as radiologists. They have learned to learn and become much quicker in daily routine with every kind of modality,' he said.

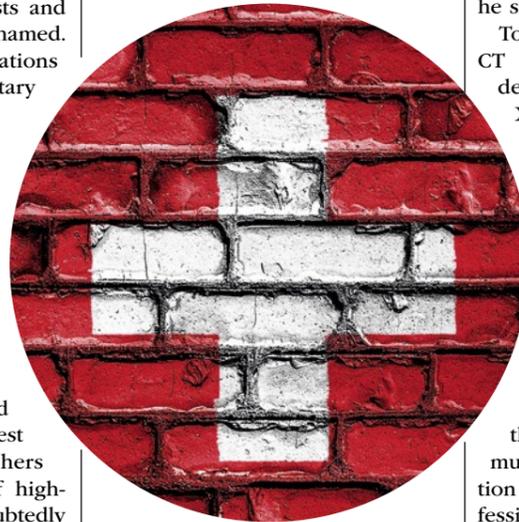
There are great advantages to having a bachelor's degree. Conversely, pathways to clinical practice with a university level cost quite a few additional years of studies and more

money. The trend for a bachelor's level is spreading through Europe and hopefully we'll follow this trend as soon as possible,' he said.

But trilingual and multicultural Switzerland is a complex setting to homogenise education. The Swiss Association of Radiographers recently fought to establish a bachelor's level on the national level, a battle lost in 2015.

## Defending their role as experts

Swiss radiographers have yet another challenge to face because, not only them but also chiropractors, medical assistants, doctors in private practices, theatre support workers, cardio technicians and nurses are entitled to perform X-ray examinations.



Trilingual and multicultural Switzerland is a complex setting to homogenise education

Meanwhile, radiographers are responsible for radio-protection, according to the Federal Office of Public Health; but they do not always have the necessary authority and time to apply the rules and safety guidelines, Jaermann argued. 'As a result, some surgeons do not respect some basic radio-protection rules, except for themselves,' he said. 'So radiographers must defend their roles as experts and must assume this role in theatres for supervising non-specialised professionals, in accordance with the law.' Radiographers also have to develop new fields of activities

The education of radiographers remains unequal throughout Switzerland: While the bachelor's level was introduced in the French-speaking zone in 2002, radiographers still take a diploma of higher education in the rest of the country

under the radiologist's supervision. For starters, Jaermann suggested letting radiographers perform ultrasound examinations, with radiologists' final approval. 'US is time consuming and radiographers cost much less than radiologists and would deliver reproducible images,' he said.

To increase their autonomy with CT or MRI, radiographers could delegate part of the standard X-ray to medical assistants. 'Radiographers would be responsible for quality and continuous professional development for these assistants. This is a new way of thinking, which might lead to discussion.'

## Stepping out of the shadow

Legislation is the ultimate battlefield for radiographers, who must be included in any legislation that regulates healthcare professions. Jaermann is convinced that the only way to do so will be to expand the bachelor's level nationally and acquire more skills.

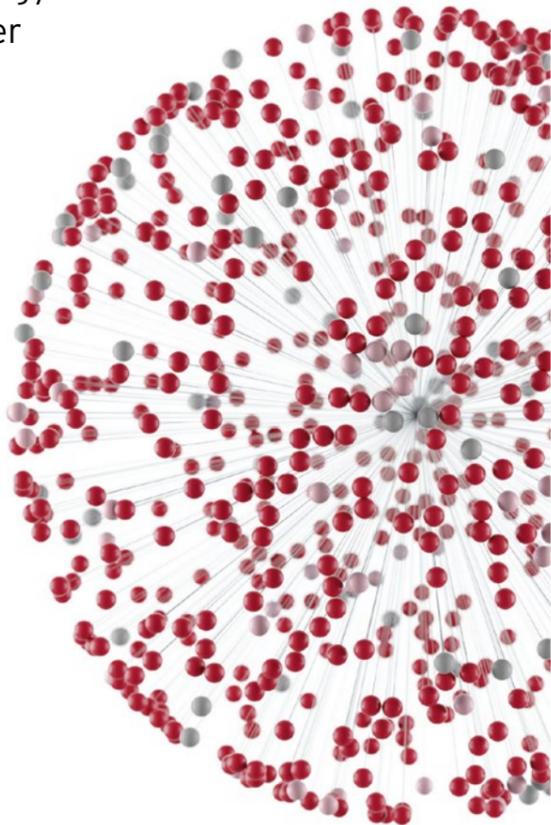
Further education will be paramount, and evolution of radiographers' training has to be in a step with the evolution of nuclear medicine, radiotherapy and radio diagnostics. 'Studying three domains is essential. With the new hybrid machines we have a foot in two or even three domains – think about radiotherapy using CT, ultrasound or even MR next,' he explained.

Finally, tighter cooperation will be mandatory to help secure changes. 'Our head radiographers must work together to support projects. And our radiographers need to be more ambitious. They have to be prouder and not live in the shadow of other professions any more,' Jaermann concluded. 'Our professional association has to intensify its political influence.'

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