VOL 30 ISSUE 2/19 • Apr/May 2019

EUROPEAN HOSPITAL

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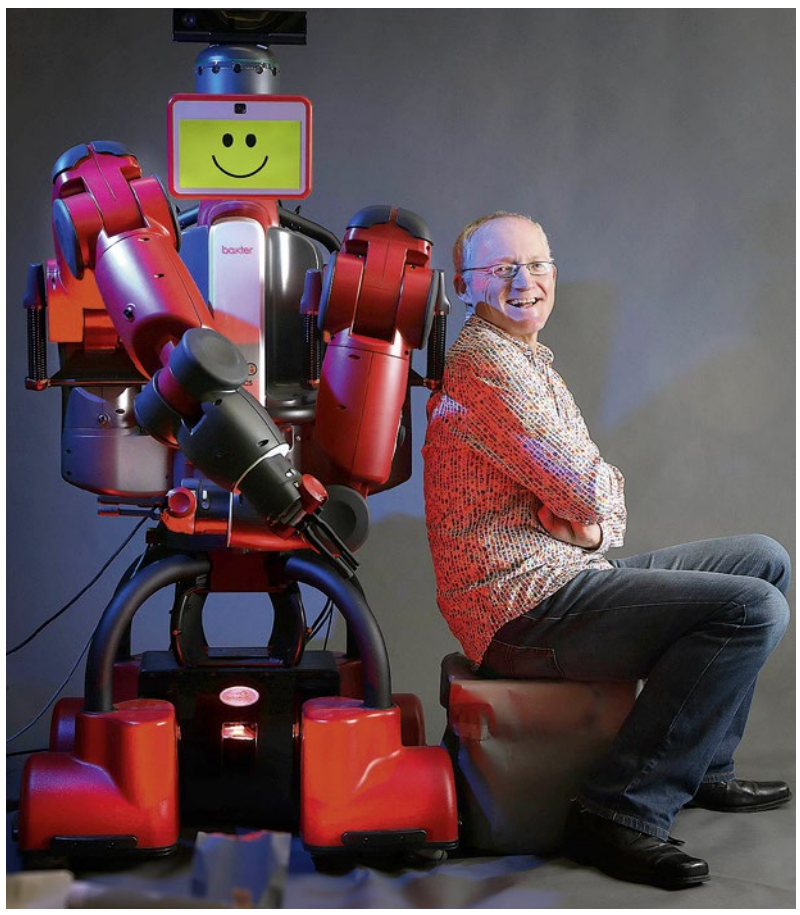
AI? We shouldn't worry about it – yet

Humanity is not doomed to submit to machines as in the Terminator movies – or at least not yet. Artificial intelligence (AI) systems are still far from capable to imitate the human brain in all its complexity. Yet there is no doubt that AI will have a global and huge impact, particularly for professionals such as radiologists, who should look at AI critically and focus on the many new opportunities that will arise, advises Australian AI expert Professor Toby Walsh.

Report: Mélisande Rouger



Will machines be taking over? No – at least not in the foreseeable future, according to AI expert Toby Walsh. While certain algorithms today come close to, or even surpass, humans in narrowly defined tasks, it should be another 50, 100, maybe even 200 years before artificial intelligence will match the complexity of the human brain.

'People have woken up to the idea that AI is going to be interesting and transformative because it will impact on every aspect of our lives,' explained Toby Walsh, a professor of AI at the University of New South Wales, speaking at the AI Premium meeting organised by the European Society of Radiology and the European School of Radiology in Barcelona.

AI will have a major impact on global economy, according to audit giant PwC, which predicted it could generate 15.7 trillion USD and account for 26.1% of GDP in China, 14.5% in North America and 10% in Europe by 2030.

'That's an inflation just in terms,' said Walsh, who is dubbed 'the rock star of the digital revolution' and has published many books on the topic. '16 trillion USD is China and India's GDP put together. It's like we've discovered a whole new continent. Last time that happened, it had big ramifications for the world's economy.' Walsh's last work, '2062: The World that AI made', is an optimistic vision of how to help mankind benefit from AI, rather than helplessly suffer the consequences

'Every profession and particularly data intensive professions, such as radiology, will be affected,' he said.

Four exponentials

Walsh shared a brief history of AI, which was boosted by four exponentials, including Moore's law, according to which the number of transistors in computers double almost every two years. This observation has accurately guided projection rates and technological developments for the past 50 years, all of which have led to immense computing power.

'Things that we dreamed about doing, we just do now because we have more computing power. We have more computing power in our smartphones than was once used to fly a man to the moon,' he observed.

Moore's law is now officially dead and scientists need to design new architecture to increase computing power. One trend is to design specified chips to do AI and do more on the device energy, he says.

Along the doubling of transistors count, there has been a doubling in data. 'We're collecting more and more data, and have the ability to store more and more data. This continues to help expand AI,' Walsh pointed out.

The third exponential was a doubling in performance of algorithms to recognise objects and limits. Back in 2010, one in 10 objects were classified properly. Since then performance has been doubled every two years, and now it recognises objects better than the average human does.

Last but not least, investment has doubled every two years over the past decade, allowing skyrocketing advances in AI.

The impact on radiology

AI started to make headlines in 2015, when humans lost against machines in a Go competition. Nonetheless, and despite all the progress made, it is remarkable how slowly the machine learns compared to humans, even with unlimited resources of time, Walsh underlined.

'There are still many things that machines can't do as well as humans, some of which are plain trivial. A robot developed by a colleague at Berkley University takes 25 minutes to fold a towel. Easy things for us are often surprisingly hard for computers. What's more, we have made almost no progress in artificial general intelligence that matches humans in their full capabilities.'

Computers can do narrow tasks, but nothing approaches the human brain yet. Machines are not going to take over anytime soon. 'We have 50, 100 or maybe 200 more years before it can match the human brain, if ever. So, we should not worry about it,' he said.

Instead, people should look into the exciting new opportunities and just learn about the field. This starts with differentiating between AI and machine learning. 'People often mix up these terms. But there's a lot more to your intelligence than learning.'

Other types of intelligence include, for instance, perception, speech and speech recognition, NLP, vision and reasoning. A lot of AI research focuses on machine learning, but much more could be done in workflow, image optimisation, etc. All these fields are interesting to explore for medical imaging.

Provocation for attention

The rule of thumb is that AI can now do most things a radiologist can do in a moment's thought. 'You can see an image and recognise it. The computer has been trained to do this. It can now also label images – i.e. a man dances dressed in black; a girl plays the violin, etc. – and that works pretty well. So, we can also start labelling X-rays,' he explained.

In 2017, AI researcher Andrew Y Ng, from Stanford University, claimed he and his team had developed an algorithm that could diagnose pneumonia at a level exceeding practicing radiologists. Such claims need to be taken with precaution, Walsh insisted, because studies may show some limitations.

'In this case researchers trained on 6,351 images and reported results on 420, but they only used frontal images and no patient history. Although the machine was more accurate on average than four human radiologists, one of them had only been working for four years. That brought down the human performance. Actually, there was one experienced radiologist who did better than the machine,' he said.

People should read through studies carefully, because obviously some authors might be looking for funding.

Caution should also prevail upon hearing provocative quotes, such as Geoffrey Hinton's famous line about stopping radiologists' training. 'Geoffrey is extremely bright, but he is also famous for saying provocative things to get people's attention. He also said that you couldn't predict more than five years out. I agree. There is still some distance to go,' Walsh concluded, 'before you can get much faith and confidence in equalling humans.'

Source: https://ai.myesr.org/app/uploads/Walsh-Toby-Kopie.png

World-renowned artificial intelligence professor at the University of South Wales and Data61, **Toby Walsh** was named by the media as a 'rock star' of the digital revolution and has been included on a list of the 100 most important digital innovators in Australia. He is the author of the books 'IT's Alive', 'Android Dreams' and the soon to be published release 'Machines That Think' and '2062: The World that AI Made'. The professor is a sought-after keynote speaker on how AI influences business, education, warfare, personal development, and finance, and more. Together with Pope Francis, he was voted runner up in the Person of the Year Award by the Arms Control Association, recognising his work in ensuring the safe use of AI in warfare.

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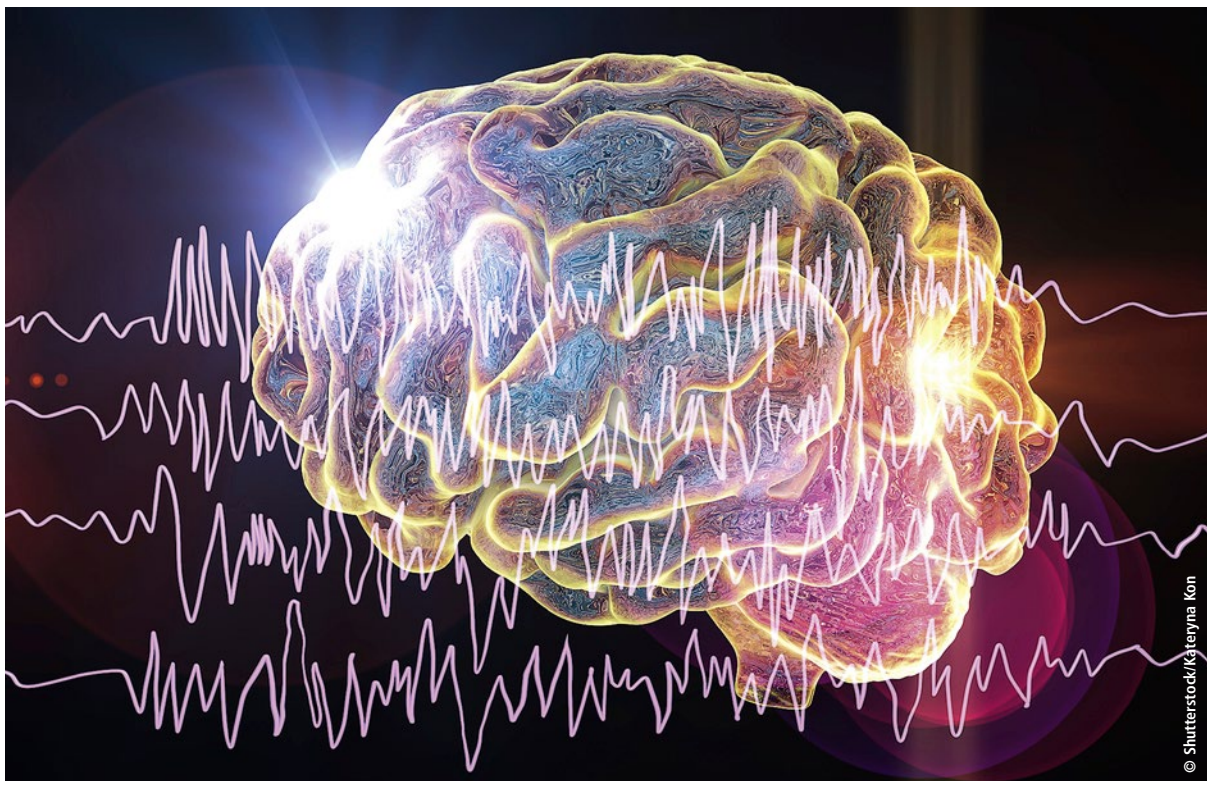
Researchers progress in predicting onset of epileptic attack

Seizure detection method brings hope

Report: Callan Emery

Epilepsy affects around 70 million people worldwide, making it the second most common neurological disorder after migraine. Epileptics bear a terrible burden because they experience recurrent seizures that strike without warning. Their symptoms range from brief suspension of awareness to violent convulsions and sometimes loss of consciousness. Epilepsy is also responsible for numerous deaths – SUDEP, or sudden unexpected death in epilepsy, occurs in about 1 in 1,000 adults and 1 in 4,500 children with epilepsy a year.

If only a device could be developed to help epileptic patients predict when a seizure is about to happen, so they could have time to prepare for it. As far-fetched as this may sound, there has been remarkable progress towards this end, and it appears the development of such a device may not be too far distant.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Over the past three decades research has been considerable to develop seizure detection systems to improve the quality of life of epileptic patients. Ideally, a system should detect a seizure well before it happens to provide a window of time for the patient to alert those around them, find a safe place to be during the seizure and potentially employ any other mitigating options available, such as taking medication. In this area, too, there have been several recent and promising developments with research into the use of cannabis-based compounds, which in early studies appear to reduce seizures.

However, this article looks at current research using electroencephalogram (EEG) data and the use of artificial intelligence (AI) to develop an algorithm that can be used to predict a seizure onset. Over the past several years there has been some interesting progress in this field.

EEG is the prime signal used to diagnose epilepsy. However, the large amount of data accumulated from EEG recording has led researchers to employ AI and deep-learning to distinguish between preictal (the time before a seizure) and ictal (the time during a seizure) EEG patterns with the aim of developing an algorithm that will show a change in EEG pattern and provide a warning of an impending seizure.

Of course, this is not a simple procedure because EEG recordings are often corrupted with several types of artifacts, including muscle activity, eye movements and environmental (white) noise. These artifacts may negatively affect the genuine manifestations of seizure patterns and severely influence the detection accuracy of epileptic seizures.

In one of the most recent studies *(Epileptic Seizure Detection: A Deep Learning Approach, Hussein R, et al., 2018. arXiv:1803.09848)* the researchers based their seizure detection experiments on the publicly available EEG dataset provided by Bonn University – the most widely used dataset for epileptic seizure detection.

They point out that 'deep learning has been proven to achieve promising results in different research problems, such as face recognition, image classification, information retrieval and speech recognition' and note that they used 'recurrent neural networks', an artificial neural network employed in AI and deep learning, 'to learn the expressive seizure characteristics from EEG data and extract the discriminative EEG features pertinent to seizures.

The researchers then tested the robustness of their seizure detection method, or algorithm, against a variety of conditions, such as seizure detection in real life which included the most common EEG artefacts. They found their algorithm could effectively and accurately 'identify EEG features associated with seizures, even when the EEG data are completely immersed in noise'.

This research by R Hussein et al. is some of the most advanced in this field. They say in their research paper that, compared to other current state-of-the-art methods, their algorithm produces significantly more robust and accurate results in effectively detecting epileptic seizures. Although no commercial epileptic seizure detection devices using EEG have yet been developed, this, and ongoing, research using EEG and AI, holds great promise for epileptic patients in that the development of such clinical devices are relatively close at hand.

Advertorial: Keeping patient workflows in mind

Designing devices as full systems

As European populations age, new medical technologies can save lives and increase both quality of life and expectancy. As hospitals and physicians continue to adapt to an increasing number of patients, new breakthroughs can also help expand treatment options. But the positive impacts cannot be fully realised unless those innovations also help clinics run more efficiently, allowing physicians to offer their patients more treatment benefits while reducing their high workloads at the same time.

That's why innovation in medical technology today should not simply be about creating devices with an ever-increasing number of impressive new features, improvements, and gadgetry – even as all those things remain important for maximising patient benefit. A new device must be conceptualised as a full system that is cognisant of the hospital environment of which it is a part. Both patient and physician must benefit from the new innovation.

The Acticor & Rivacor family of ICDs and CRT-Ds is an innovative cardiac system designed with the needs of both patients and physicians in mind.

Biotronik's new Acticor & Rivacor family of ICDs and CRT-Ds offer some encouraging examples of such a design evolution. The first of these is a greatly extended battery life of up to 15 years for the Berlin-based company's new ICDs,[1] and up to nine years for its new CRT-Ds.[2]

A longer-lasting battery likely means fewer replacement procedures, benefiting both doctor and patient. 'If a device doesn't last, that means in time you're going to have more procedures,' says Dr Iain Matthews of Northumbria Healthcare in the UK. 'More procedures mean greater risk to the patient and greater cost to the healthcare system. So, a device that lasts as long as possible is one of the most important things.'

As well as reducing implantations, the new line also eases them. 'The slim, rounded shape not only makes the patient feel much more comfortable, it also simplifies the implantation procedure,' says Dr Florian Blaschke, Head of Device Therapy at the Virchow Clinic of Charité Berlin.

The Acticor & Rivacor family is also approved for full-body MRI scanning at 3-T strength. Dr Victor Sanfins, a cardiologist at Senhora da Oliviera Hospital in Guimarães, Portugal, says while the system offers patients greater access to MRI scanning, the MRI AutoDetect feature helps clinics to avoid the extra workloads to which features can sometimes contribute. 'With great advances in high-resolution imaging with 3-T MRI, patients are undergoing MRI scans at an increasing rate. Consequently, there is a greater burden on clinics that have to re-program ICDs and CRT-Ds before and after patients go in for MRI scans,' Sanfins points out. 'With MRI AutoDetect, we can cut down on some of these re-programming steps, ensuring optimal therapy for the maximum amount of time, while also reducing the burden on patients, cardiologists and radiologists.'

1 Acticor/Rivacor VR-T Standard conditions. 15.4 years @ 40 ppm; 0% pacing @ 2.5V/0.4ms; 500 Ohms; 2 max. energy shock/year. Data on file

2 Acticor/Rivacor HF-T QP, 9.3 years @ 60 ppm; RA 15%, RV/LV 100% pacing, RA/RV/LV @ 2.5 V/0.4 ms; 500 Ohms, 2 max. energy shocks/year. Data on file

Towards

'The integration (in 2016) of the expertise from Fresenius Medical Care (FME) and Xenios (and thus the combination of the companies' competencies, strongly enhances treatment options in critical care within the intensive care unit (ICU) of hospitals across the world,' reports FME, which specialises in the provision of products and services for chronic kidney failure care.

'End-Stage Renal Disease (ESRD) almost always involves other organ systems. Pulmonary, cardiac, and hepatic failures are the most frequent diagnoses encountered by a nephrologist; acute renal failure is frequently associated with respiratory or cardiac failure,' FME points out.

Complementary products

'Xenios, located in Heilbronn, Germany, was formed in 2013 by combining the two brands Novalung and Medos under the Xenios umbrella,' the report continues. 'Novalung was founded to create new solutions for the treatment of acute and chronic lung failure. The Novalung therapy can replace or supplement Invasive Mechanical Ventilation (IMV) and prevent ventilation-associated lung damage.

'Medos was acquired to harness its innovative pump technology.

Data and information can off-set physician burnout

Digitisation pushes and prevents burnout

Report: Mark Nicholls

Deployment of electronic health records (EHR) are increasingly cited as a factor in physician burnout. However, a senior figure with the Healthcare Information and Management Systems Society (HIMSS) – which supports the transformation of health through information and technology – believes defined use of data and information can help off-set the impact of burnout among health professionals. 'Physician burnout is often said to be caused by digital transformation,' HIMSS Chief Clinical Officer Dr Charles Alessi said. 'If the deployment of an EHR is badly handled, this can be the case, but there are plenty of other reasons why burnout is a problem.'

His lecture 'Managing Physician Burnout: Using the EHR as a Clinical Extender' delivered during the HIMSS Global congress in Orlando, Florida last February, focused on causes and solutions whilst acknowledging the issue of physician burnout – which encompasses emotional exhaustion, depersonalisation, distress and depression – remains serious.

The session came as new data emerged from Mayo Clinic that physician well-being was improving, though he pointed to broader research that still suggests 50% of physicians, in practice across all disciplines or in training, are affected, along with nursing cadres and other health and care workers.


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Causes, he said, range from 'doing more with less', increased thought output and manpower issues. They include changes brought about by the democratisation of information allied with the consumer revolution; the requirements of clinicians to both manage and exclude clinical risk at the same time and with the same patient; and the increased administrative burden associated with payments and assurance, as well as 'less than optimal' EHR deployments.

While there are 'no simplistic solutions', Alessi said mitigating measures can be taken and that the EHR has a part to play in helping to address the issue of physician burnout.

'The data and information can play a significant role in managing burnout if applied correctly. A use case is one I introduced personally into my general practice in England, where we had teams of people looking after populations. This meant we had doctors and nurses working in a way where the continuity of care was delivered via the clinical records.'

He outlined how his practice instituted a system whereby they monitored the time patients spent with each clinician and the wait before they were seen, the backlog of letters to be managed, the number and waits associated checking lab results, and the number of visits awaiting completion.

'This gave us a view of how well each individual was managing with the workload,' he continued. 'When we noted deteriorations in performance, we immediately instituted a process where we offered extra support – such as reduced workload till they caught up. This both identified impending problems very early and put in remediation immediately. We did not have a single episode of burnout in the years that followed, despite increasing workload and throughput as well as serial introductions of new EHR processes.'

He suggests the EHR can be used as a 'clinical extender' in this context; as the vehicle to communicate with the patient, with the important issue being to try to keep that connection as personal as possible between patient and clinician, such as using a named person to communicate.'

However, he stressed the importance of thinking carefully before deployment of new systems and taking the perspective of the clinical staff into account as well as that of the administrative staff and patients.

Evidence remains that EHRs contribute to physician burnout, such as from a 2017 study published in the Annals of Family Medicine (AFM) which found that primary care physicians spend more than 50% of their time working on tasks associated with EHRs instead of caring directly for patients.

A similar 2016 study published in the Annals of Internal Medicine (AIM) found that 'for every hour physicians provide direct clinical face time to patients, nearly two additional hours are spent on EHR and desk work within the clinic day' with further tasks performed outside office hours.

Dr Charles Alessi is Chief Clinical Officer for the Healthcare Information and Management Systems Society (HIMSS); senior advisor to Public Health England and lead around dementia and ageing. He is also a former Chair of the National Association of Primary Care in England (the national body representing the hospital sector including primary care). The HIMSS is a global advisor and thought leader supporting the transformation of health through information and technology.

In a recent Mayo Clinic update – based on extensive research on physician burnout – findings suggest physician well-being is improving, but physicians remain at high risk for burnout, depression and depersonalisation, compared to other professionals.

Researchers from Mayo Clinic, the American Medical Association and Stanford University collaborated in the national survey of physicians across more than 20 specialties to assess any changes between the previous study in 2014 and the original survey in 2011. While burnout varies by specialist, overall reported levels of burnout and satisfaction with work-life integration improved between 2014 and 2017 – but only to 2011 levels.

More than 30,000 physicians were invited to participate in the electronic survey; just over 5,000 responded.

Researchers say the reason for the change may be due to physicians adapting to the new work environments over the three-year period. Also, much progress may be attributed to interventional programs to stem burnout in hospitals and other facilities.

How a strong complementary merger pays off

s multi-organ support

Supplying this technology to cardiac surgeons and perfusionists, Medos was one of the leading German companies in this field since 1987. This acquisition enabled the company to expand its overall product portfolio to offer both heart and lung support on one single platform: the Xenios console.'

'Xenios' dedication applies to the welfare of patients. Especially Novalung therapies provide fundamental advantages to patients: physicians and caregivers can keep them awake, mobile and self-determined which facilitates improved outcomes.

'The combination of Xenios and FME therapies empowers clinicians with the tools required to practice true interdisciplinary care in the ICU for the benefit of seriously ill patients. Many are already receiving renal therapy prior to the need for heart and lung assistance.'

The next step: multi-organ support

'By entering the treatment of cardiac and pulmonary diseases via Xenios, FME is expanding and strengthening its leading position in the area of extracorporeal organ support,' the firm continues. 'Treating heart and lung diseases with extracorporeal therapy systems is closely tied, of course, to dialysis – both in technical terms and in the clinical process.

'Together with Fresenius Medical Care we are creating a perfect synergy between FME's expertise in renal support and Xenios' expertise in heart and lung support. We are taking the next step towards multi-organ support,' Dr Andreas Terpin, CEO of Xenios AG, added.

'Xenios and FME already implemented their technological collaboration by connecting the Xenios console via the iLA active iLA kit IPS to the MultiFiltratePro from FME. 'During dialysis, a CO_2 removal for lung support can be carried out simultaneously, combining renal and lung therapies,' the FME report continues. 'Consistently pursuing a holistic multi-organ approach, FME aims to establish worldwide market leadership from renal to heart and lung assist.

KIMES 2019: Stable relations have been laid'

Korea? It's all about the future

The 35th Korea International Medical & Hospital Equipment Show (KIMES) again proved to be a great success. Over 73,000 visitors from 96 countries entered the show in Seoul, attracted by, for example, the latest developments in AI-assisted diagnostics, robotic surgery and rehabilitation, healthcare solutions for the aged and comprehensive smart hospital systems.

The KIMES motto, 'Meet the future' was apt: 40,500 square metres of exhibition space, saw innovations that could have been classed as science fiction not long ago. Today, such innovative radiology, laboratory and surgical devices and tools, medical software, rehabilitation technology are a reality.

More than 1,400 companies from 36 countries were represented, including the important industrial nations in Asia, Europe and the US. Emerging markets, such as the Near East, the Commonwealth of Independent States and Africa, also played important roles.

Local actors play key parts

The organisers of the fair, Korea E & Ex Inc., saw the rising number of visitors and exhibitors as a clear sign of the sustained relevance of KIMES and the growth potential of the Asian medical market as a whole. 'As a leading medical event in the Asian region, we can continue to grow and act as a central hub for all players in the medical and healthcare industry,' the organisers added.

Local manufacturers, such as Samsung, Listem, DK Medical, BIT Computer and Alpinion were great lures, alongside international competitors such as Fuji, GE, Philips and Shimadzu. Visitors were noticeably interested in the innovations shown, including solutions in robotics, 3-D printing, wearables and smart analysis tools.

Greater variety of topics through cooperation

Amongst the most important new features at KIMES 2019 was the cooperation with Medical Korea, a conference focusing on global health and medical tourism. The organiser, Korea Health Industry Development Institute, also contributed to the success of KIMES 2019 with presentations on service topics, global trends, developments, medical training and development of new (digital) markets.

KIMES acknowledged the growing importance of technologies around artificial intelligence (AI) by hosting the co-event MedicomteK,

which focused on AI and deep learning developments as well as the manufacture of high-tech medical products which continue to be very much in demand.

180 lectures deliver knowledge

Along with the innovations presented at the exhibition stands, KIMES again excelled with around 180 top-class, specialist lectures and seminars, the organiser adds. Highlights this year included the keynote from Bidur Dhaul, who is responsible for the Patient Care and Monitoring Systems divisions at Philips Health Tech. Dhaul provided his large audience with insights into the latest developments in the field of smart care solutions.

Further sessions addressed the role of healthcare politics in the medical devices market, cutting edge technologies and financing solutions for doctors.

'The concept behind KIMES paid off once again this year,' Korea E & Ex Inc. confirmed. 'Stable foundations have been laid for the future of this Korean show.'

Island show never fails to surprise and delight

Medical Taiwan 2019 – this j

Artificial intelligence clinics and rehab bikes, exoskeletons and stylish protections masks – healthcare in Taiwan has many faces and facets as the international medical & healthcare exhibition Medical Taiwan in Taipei will show from June 27 to 30, 2019. We visited participating companies and hospitals for a preview of some of the highlights that might well create a buzz in Europe.

Report: Wolfgang Behrends

From important basics to hypermodern technology Medical Taiwan covers the entire gamut the island's healthcare industry has on offer. The country is considered a trail blazer in technology and thus expectations are high. However, the exhibitors are confident that their innovations will once again wow the audience.

Case in point: Wistron Medical, OEM producer for partner companies. One of their highlights is BestShape, a Big Data-based software solution for the predictive analysis of dialysis values. 'Arterial hypotension is one of the most common and most dangerous complications in dialysis patients,' Brian Chong, Vice President of Wistron Medical, pointed out. 'Our tool can reliably predict such sudden episodes and thus help save lives.' The software sends HL7-data automatically to the HIS and thus avoids the errors so frequent in manual transcription.

Same company, entirely different product: the exoskeleton Keeogo, designed for patients with diseases-related muscle weakness, e.g. multiple sclerosis or Bekhterev's disease. Keeogo can also be used as a rehab tool for patients who suffered a stroke or underwent surgery. The computer-supported orthosis is equipped with fine-tuneable engines that amplify movements to facilitate everyday tasks such as walking, jogging, climbing stairs, sitting down and getting up.

Award-winning mobile ECG

Products that were awarded the prestigious label 'Taiwan Excellence' will be prominently displayed at the exhibition. BriteMed's mobile 12-lead ECG is one of these outstanding innovations. 'Since it is easily portable, our ECG device is well suited for first aid and it enables precise cardiac diagnostics even in remote areas,' said Kelly Wang, Senior Marketing Manager of BriteMed. The latter aspect caught the attention of the Taiwanese health ministry which aims to improve care in rural areas. The device features a sophisticated shield that protects it from damages caused by defibrillators and thus makes it well-suited for emergencies. Moreover, BriteMed will present its medical-grade displays and instrument carts.

The 12-lead mobile ECG from Taiwanese manufacturer BriteMed was awarded the Taiwan Excellence label

AI in the ICU

While many experts still wonder how to use blockchain in healthcare, the Taipei Medical University Hospital (TMUH) has already integrated this technology in its processes. iWellChain helps to create electronic medical records that contain all relevant healthcare data and makes them available to different facilities in digital form. Blockchain is also used in so-called Smart Contracts, inter alia to automate invoicing or to process insurance claims.

Patient data plays a crucial role in TMUH's AI-supported monitoring system. 'It monitors and assesses the vital signs of our ICU patients around the clock,' explains Dr Kuo-Ching Yuan of the hospital's ICU. Physicians and nurses can view clinical values, image data and diagnoses in easy-to-read charts and thus always have up-to-date information on the patient's status. 'This technology has significantly improved the quality of ICU care,' Yuan confirms, adding: 'response times to critical events were reduced by several minutes and the number of bloodstream infections decreased by more than 60 percent.'

Ready to tone with clothing - colourful face masks produced by CSD

Additionally, AI-support reduces length of stay in the ICU and lowers treatment as well as administrative costs. The system learns from the data collected: 'Going forward, we want to use the system for risk assessment, for example to predict bacteraemia or sepsis.'

Mobile, resilient, stylish

Taiwanese manufacturers can do more than high-tech. At Medical Taiwan, for example, Pacific Cycles will present adaptive bikes designed to support muscle build-up and coordination after a stroke. Other models aim to help patients with cerebral palsy and similar conditions. 'If need be, we can make bespoke bicycles because each customer has highly individual needs and requirements,' explained Daniel Tsai, sales rep at Pacific Cycles. An eye for detail and a focus on resilience are two features of Grand Tree, a manufacturer that will present medical mountings and monitor arms in Taipei.

Another provider of medical components is QS Control Corporation (QSCC). This company offers a wide range of products, from parts of dialysis systems to laparoscopic instruments, orthopaedic screws and implants.

Closing the gap between fashion and healthcare is the mission of China Surgical Dressings (CSD). The company will add style to the previously strictly functional mouth and

Speeding up assessment of clinical risks

The digital early warning system

Staff shortages are among the most urgent healthcare problems. While digitisation might offer relief, unfortunately many hospitals lag behind in transforming their processes. As pressure mounts, the chorus is heard: 'It's high time for bold changes'. Indeed, this was the motto of the 2019 Western German Health Congress held in Cologne, an event that focuses on health policy and health economy in this area. There was also a focus on how to inject energy into the sluggish approach to digitisation.

Report: Beate Schenk

According to estimates by the German Hospital Federation the country's healthcare system could save a whopping €34 billion annually, half of this in hospitals, if the potential of digitisation were to be fully realised. Non-digitisation not only means loss of income, but also possible loss of lives, particularly in emergency care. 'Unexpected events and the deterioration of the patient's status must be recognised early – one of the core life-saving tasks on any hospital ward. We have many multimorbid patients. On average, 20% of them suffer a severe incident,' said Bernd W Böttiger, Director of Anaesthesiology and Surgical Intensive Medicine at University Hospital Cologne. 'To avoid such incidents emergency care guidelines explicitly demand monitoring vital signs and responding to emergency calls quickly.

Philips IntelliVue Guardian with Early Warning Scoring is a customisable patient monitoring system combining software, clinical decision support algorithms and mobile connectivity. Used in a general ward, this helps to identify subtle signs of deterioration in a patient's condition hours before a potential adverse event occurs

Early warning, quick response

To recognise, or even better, avoid signs of a patient's clinical instability despite tight staffing, Sana Klinikum Lichtenberg in Berlin introduced IT-supported Early Warning Scoring (EWS) to its abdominal surgery department. After successful completion of the pilot phase, EWS is now in regular operational mode. EWS is based on the vital signs: blood pressure, pulse/heart rate, body temperature, oxygenation and assessment of consciousness level. These parameters are regularly recorded by the nurses. When the score deviates, which might indicate a change in patient status the medical team are alerted via smartphone in a cascading alarm system, enabling immediate response.

Wireless sensors can be set to individually configurable time intervals, which allows tighter and site-independent monitoring and control of the vital signs without putting an additional burden on the nurses. Early warning systems that alert the medical team to problems significantly improve the quality of care.

The vital signs of all patients in the 34-bed department of general and abdominal surgery are measured and recorded digitally twice a day. 'The procedure takes about one minute per patient,' said Ivonne Lemke, interim head of nursing. 'The team records many more parameters than before,' she added.

Digital cost reduction

The Clinic of Anaesthesiology and Surgical Intensive Medicine at University Hospital Augsburg also uses an IT-supported early warning system. Wireless measurement devices, mostly cuffs, record vital parameters at individually set intervals and continuously transmit values to a central monitor in the nurses' station – entirely independent of a patient's location – even if monitored in their home. Frequently, certain vital parameters start to deteriorate 48 hours before the actual clinical deterioration. Depending on the type of values recorded, and the given risk pattern, the physicians or an emergency team is automatically notified. Whenever the early warning system indicates deterioration of vital signs, the nurses monitor the patient more closely and can initiate measures proactively.

When the ward cannot provide a recommended treatment, the patient can be moved to the ICU. Unnecessary moves, on the other hand, can be avoided – which reduces costs. 'Per one thousand patients we see a significant decrease in emergency calls and circulatory arrests. Thanks to clearly defined early warning criteria the absolute number of necessary reanimations is on a low level – despite increasing severity and increasing number of patients,' explained Professor Axel R Heller, Director of the Clinic of Anaesthesiology and Surgical Intensive Medicine at University Hospital Augsburg.

Heller plans to use digital measurements systems more often in research: 'With Smart Data, meaning the intelligent use of large data volumes, we can make real progress in anaesthesia and intensive medicine, in research as well as patient care, above all regarding early detection of patient risks.'

Professor Axel R Heller is Director of the Department of Anaesthesiology and Intensive Care Medicine at the University Hospital Augsburg. Previously, he chaired the Department of Emergency Medicine at the Technical University Dresden. He is an expert on the practical implementation of clinical research, including digital solutions for anaesthesiology and the ICU.

Professor Bernd W Böttiger is Director of the Department of Anaesthesiology and Intensive Care Medicine at the University of Cologne. His work focuses on emergency medicine and promoting knowledge of resuscitation basics among the general public. He is also Director of Science and Research at the European Resuscitation Council (ERC), CEO of the German Resuscitation Council (GRC) and a board member of the German Interdisciplinary Association for Intensive and Emergency Medicine (DIVI).

June

nose masks widely used in Asian countries outside healthcare.

CSD offers masks not only in the usual hospital colours of white and turquoise, but many other hues, and even popular denim.

A famous Taiwanese pop singer wore one of the masks in her most recent music video. The manufacturer, who also produces surgical gowns, medical-grade gauze and disinfection swipes, has even partnered with fashion magazine Elle to issue a special 'Parisian' edition of products with Eiffel tower prints. While in Europe these products are still few and far between, Asian exhibition visitors will most likely be delighted by the fancy masks.

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Liquid chromatography/mass spectrometry for clinical labs

Calling for easy-to-use plat

LC-MS is an established powerful tool in routine clinical use and clinical research. However, to further capitalise on its benefits, instrument and consumables vendors should continue to improve accessibility and ease-of-use, according to Dr Debadeep Bhattacharyya, senior marketing manager for clinical and forensic at Thermo Fisher Scientific.

Remarkable advances in analytical technologies have had a profound influence on human health over the past few decades, and mass spectrometry (MS) is by no means an exception. MS has been in existence for over a century – its fundamental principles were first described by Nobel laureate Sir Joseph John Thomson in 1897. Despite some initial research on the use of MS for respiratory gas analysis in the 1950s, its clinical history is often considered to have started in the early 1970s with its use, alongside gas chromatography (GC), to determine various biologically significant molecules. However, because GC requires a certain level of analyte volatility and since many biologically active molecules are polar and thermolabile and have low volatilities, elaborate extraction and derivatisation protocols had to be devised to enable their separation and detection, limiting the usefulness of GC-MS for the analysis of clinical samples.

LC-MS as a clinical tool

Liquid chromatography (LC) is a powerful technique to separate polar and thermolabile molecules, and its use, in combination with MS, has grown in clinical laboratories over the last 10–15 years. The widespread adoption of LC-MS for quantitative assays in large part is due to its improved specificity and selectivity over immunoassay techniques and the ability to combine multiple analytes into a single run *[Jannetto PJ, Fitzgerald RL. Effective use of mass spectrometry in the clinical laboratory. Clin Chem 62, 92–8 (2016)]*. Furthermore, the lack of availability of immunoassay kits for certain analytes and lot-to-lot variability of some commercially available immunoassays has led growing numbers of analytical laboratories to turn to LC-MS *[Hoofnagle AN, Wener MH. The fundamental flaws of immunoassays and potential solutions using tandem mass spectrometry. J Immunol Methods 347(1-2), 3-11 (2009)a]*.

The LC-MS approach most commonly used for clinical applications utilises LC coupled to triple quadrupole mass spectrometers (LC-MS/MS). These methods involve the ionisation of analytes, which are subsequently separated and selected according to their mass-to-charge (m/z) ratio. These initially-formed or 'parent' ions are then broken into fragments, detected and analysed to generate information about the original analyte's structure. Among the earliest applications of quantitative LC-MS/MS was therapeutic drug monitoring (TDM). One of the major advantages of LC-MS over immunoassays for TDM is the ability to address multiple analytes in a single run *[McShane AJ, Bunch DR, Wang S. Therapeutic drug monitoring of immunosuppressants by liquid chromatography-mass spectrometry Clin Chim Acta 454, 1-5 (2016)]*.

LC-MS is also used extensively for other applications requiring small molecule quantitation, such as toxicology, endocrinology and new born screening. Today, the use of LC-MS for both laboratory developed tests (LDT) and clinical research applications continues to expand, from automated sample handling applications to the analysis of new sample types and analytes, including those in translational proteomics and metabolomics.

Operational nuances

Despite the many advantages of LC-MS, its adoption in routine clinical work has been hampered by the need for a high level of technical expertise required for operation. Successful use of LC-MS/MS relies on careful selection and adjustment of a number of operational modes and settings, including ionisation technique (e.g., electrospray or chemical ionisation), fragmentation processes, and transition and scan parameters. Subsequent data analysis and reporting steps can also be complex and need specialist knowledge for optimal outcomes.

In addition to specialist knowledge around instrument operation, a high level of expertise is often required for the preparation of samples prior to injection into the instrument (such as protein precipitation, liquid-liquid extraction and solid-phase extraction). Optimal selection and application of calibrators help maximise the accuracy of the targeted quantitative assays.

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Indispensable blood transfusions are safer than ever

Donor organ becomes immunologically invisible

Report: Anja Behringer

The safety of blood transfusions is questioned again and again by the mass media. Sometimes 'bad' blood causes infections; sometimes a transfusion leads to cancer years later. The fact is that transfer blood is subjected to the highest safety standards – there are very clear statutory regulations. Nonetheless, there will be shortages because, given increasing longevity, the proportion of older patients that need blood is significantly higher.

At the same time a willingness to donate blood is declining: the share of whole blood donors among the general population dropped from 3.3% to 2.8% between 2008 and 2016. Moreover the proportion of younger people among the total population is declining and, starting at 68, a physician must decide whether a blood donation is possible.

The future need for blood reserves can hardly be predicted. Medical progress will reduce the demand for blood products due to refined operative techniques and new medicines in cancer therapy, but the demographic development will lead to an increase in illnesses needing n blood transfusion, e.g. cancers and thus increase the need for blood.

Donor blood safety

At the annual meeting of the German Society for Transfusion Medicine and Immune Haematology in Lübeck, all aspects have been discussed. Blood donation can save lives. However, a potential risk is that pathogens can be transmitted. To keep this risk as low as possible, blood products are tested or treated for the most important pathogens, so that possible viruses or bacteria can be deactivated. An infection due to a transfusion is extremely unlikely. 'Blood transfusions are safer today than ever,' confirmed Professor Holger Hennig, deputy director at the Institute for Transfusion Medicine of the University Hospital Schleswig-Holstein in Lübeck and president of the DGTI congress.

In Germany today, especially due to the molecular biological testing applied, it is extremely unlikely that a dangerous viral infection can be transmitted through blood products. Thus the risk that human immune deficiency virus (HIV) is transmitted through a blood transfusion is less than 1:25 million. The probability of infection with hepatitis C viruses (HVC) through foreign blood is even less than 1:75 million and only around one in eight million blood units is contaminated by the hepatitis B virus (HBV). 'This number will probably decline even more in the coming years,' Hennig explained. 'Since the 1990s, the vaccine calendar calls for HBV immunisation in childhood.'

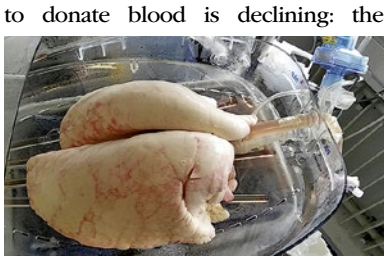
However, the introduction of ever-newer tests generally collide with financial and organisational barriers – already the introduction of the HEV (Hepatitis-E-Virus) tests, since 2013, when individual cases of virus transmission through blood transfusion were registered, is keenly debated by experts. Therefore transfusion medicine is facing a change in thinking away from specific testing for individual pathogens and towards the general deactivation of pathogens in blood products.

Specific tests are also avoided when dealing with exotic pathogens that can enter the country with travellers. Instead those willing to donate, who return from a region with a high infection risk for e.g. malaria or Zika, the West Nile or MERS virus must maintain a 'quarantine' of four to six weeks before they can donate blood again. Furthermore, the guidelines of the German Federal Physicians Association very strictly govern the use of blood in therapies with blood components. Today's patient blood management also involves taking numerous other measures to prevent the need for transfusions. Hence potential anaemia is already treated prior to surgery. During the operation every effort is made to re-use the patient's blood as much as possible.

Invisible organs against organ rejection

Patients need lots of blood, especially in connection with organ transplantations. This means that the risk of organ rejection must be kept as low as possible. Therefore Professor Rainer Blasczyk of the Institute for Transfusion Medicine of the Medical College Hanover works with his team on a method of organ engineering, which leads to organs that are invisible to the recipient's immune system.

In this future scenario, currently being tested on large animals, avoidance of rejection is to significant-



Lungs (from Minipig) in an ex vivo perfusion device after successful genetic organ engineering whereby they have been so altered that they are largely invisible for the recipient's immune system

forms

Moreover, the choice of LC columns and eluent profile is also critical for the separation of the analyte of interest from isobaric or non-specific interferences, and avoiding ion suppression.

Improving accessibility and support for users

The operational nuances of LC-MS technologies, workflows and applications, together with the expected future analytical demands, all point towards the need for smart and easy-to-use platforms that help users overcome their analytical challenges and achieve their scientific and business goals.

Thermo Fisher Scientific is enabling implementation of LC-MS technology in multiple environments with an optimal combination of analytical instruments meeting a range of regulatory requirements (Research use only [RUO] to Class I and Class II – product availability in each country depends on local regulatory marketing authorisation status), easy to use software, and superior application and service support,' says Bradley Hart, Senior Director, Clinical Research, Chromatography and Mass Spectrometry Division at Thermo Fisher Scientific. 'This provides customers choice and flexibility for solutions to cover the broad range of analysis for a variety of clinical applications.'

From Class I medical devices and Class II clinical analysers through to novel sample preparation options and instruments designed for research use only, there is a broad choice of platforms and solutions that meet the needs of individual applications, analysts, and organisations. Expansive databases, methods and workflows that facilitate and add value to research, as well as intuitive software solutions that can be seamlessly integrated with existing laboratory information management systems, are helping laboratories reach their goals in the shortest possible timeframe.

With prompt support and effective training from instrument and consumables vendors, clinics and other organisations use their resources more efficiently and gain more from their teams. For clinical laboratorians and researchers to be confident of the integrity of the technologies they buy and use, and the data they obtain from them, it is imperative that vendors of LC-MS devices and consumables meet the needs for routine clinical, lab developed tests as well as research apps.

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In 1998, a year after physician **Rainer Blasczyk** completed his aggregate in transfusion medicine at the Charité, Humboldt-University Berlin, he was appointed university professor and director of the Institute for Transfusion Medicine at the Medical College in Hanover. In 2009 he became a member of the Scientific Committee of the European Federation for Immunogenetics and, from 2014 he has been a member of the management board of the Integrierten Forschungs- und Behandlungszentrums Transplantation (IFB-Tx) of the MHH, which receives funding from the Federal Ministry for Education and Research (BMBF). For the past four years Blasczyk has been active in the 'Blood' working group at the Robert Koch Institute, German Federal Health Ministry.

ly increase the number of available organs by making re-transplantation less frequent. Until now the basic idea for avoiding a rejection has always been to modify the recipient's immune system to attain an immunological blindness towards the transplanted organ, usually at the expense of life-long immunosuppression. Now the research objective has been completely reversed – to make the donor organ immunologically invisible.

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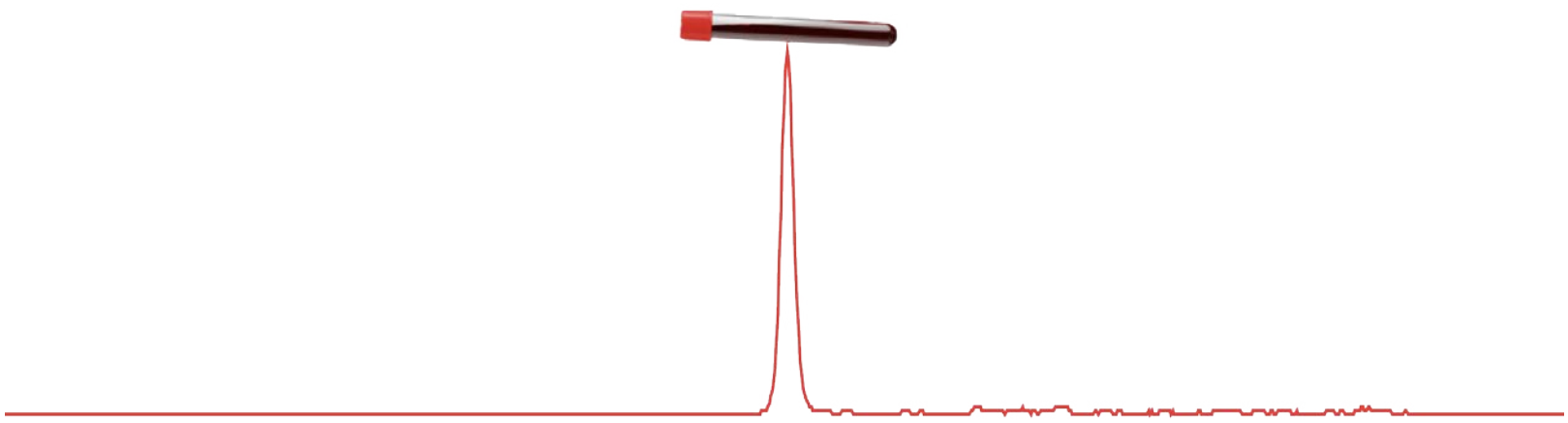

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Old age is not about being young

We need a Senior Laborat

It's undeniable: the bulk of our population is growing older. Yet, this demographic change has not altered laboratory medicine: the reference values for many analyses are still based on data of a younger cohort. Inevitably this could lead to serious errors in the interpretation of older patients' test results. Professor Kai Gutensohn, Managing Director and Medical Director of AescuLabor Hamburg, Germany, points out some of the differences between old and young – and how these should be reflected in lab diagnostics. Daniela Zimmermann reports.


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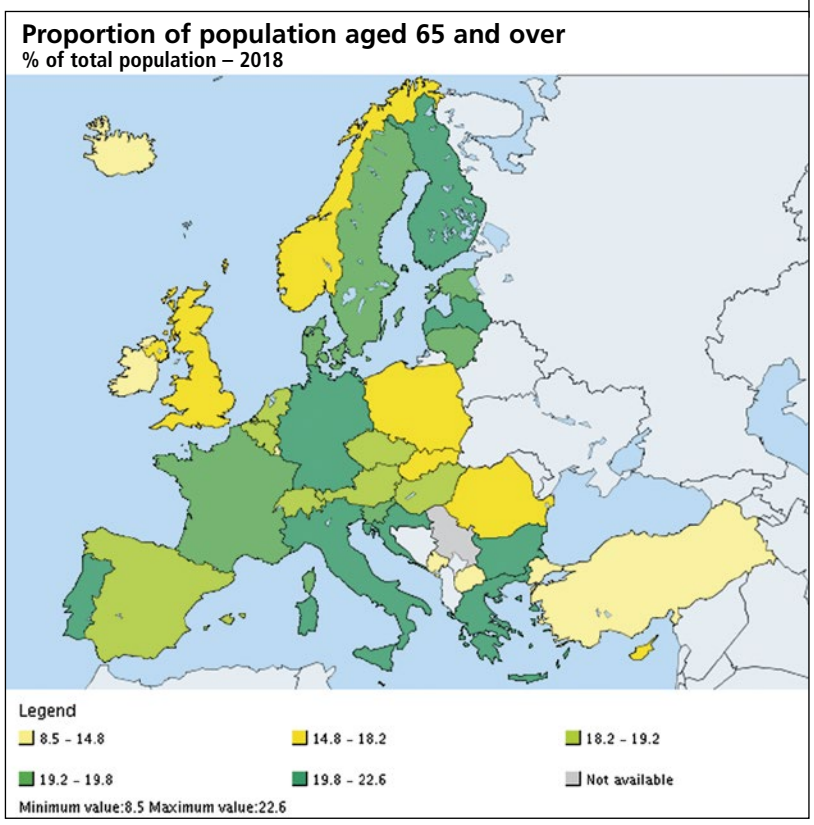
According to European Commission statistics for 2017, the 65+ age group currently accounts for around 19.5 percent of the EU population. This percentage will increase and it is expected that particularly the number of octogenarians will rise dramatically over the next few decades. 'This shows how urgently we need geriatric medicine,' says Dr Kai Gutensohn. 'In these age groups, many diseases manifest themselves quite differently than among younger people – which makes correct diagnoses so much more difficult. Lab medicine needs to address the topic of ageing in quite a fundamental way. What we need is a kind of *senior lab*.'



One basic problem is reference values: 'Lab analytics defines ranges that are considered the 'norm'. However, these values are mostly generated from 20 to 40-year-old patients. This raises the question of whether the reference values in labs are applicable to older age groups.' In haematology, for example, age-specific values were established for the age group 1 to 18, but not for older patients. This is even more alarming, Gutensohn explains, in view of the very significant differences, for example, between 'young old people' (65-74 years), 'aged' (75-84) and 'elderly old' (85+). He also points out: 'There is only a weak correlation between the date of birth and biological age.' This affects, among others, pharmacokinetics and pharmacogenomics, since many drugs show different effects in younger and older bodies.

Multimorbidity and polypharmacy broaden range

Significant differences between old and young can also be traced back to the higher prevalence of chronic diseases and multimorbidity as Gutensohn says: 'In many over 65-year-old patients three or more conditions coexist.' In older patients, the main causes for consulting a physician are dizziness and shortness of breath, followed by heart issues and back pain and well as blood pressure issues. All these can be caused by a number of age-typical conditions such as diabetes mellitus, heart disease, hypertension, diseases of the bones and tissues, arthritis, bronchitis and 'flu. Multimorbidity often leads to concurrent use of multiple medications – thus polypharmacy has to be considered in the diagnostic work-up of older patients.

To a great extent patient age determines the kind of relevant tests in lab diagnostics: 'For children and young adults basic lab tests, allergies and certain microbiological tests are common. However, in the 65+ patient group the focus is more likely to be on haematology, protein diagnostics, medication level and auto-antibody testing.' Moreover, prevention becomes an important issue, for example measuring glucose and lipids for diabetes prevention of screening for malignant diseases. PSA levels might indicate prostate cancer. The reference values, however, are clearly age-dependent and if age is not fully considered the wrong treatment or therapy might be prescribed.

High Sensitivity Troponin I assay improves cardiac care

Rapid myocardial infarction verification

The use of troponin assays to rule in or rule out myocardial infarction (MI) rapidly is critical on several levels. The quick result can reassure the patient that they have not had a heart attack and can return home safely; or, in the event of MI, the relevant treatment can start very soon. It also ensures that clinicians can make the right decision with confidence.

Troponin levels have been the traditional biomarker for diagnosis of MI for a number of years but, in a new era of the assay, greater sensitivity has been delivering improved results.

Clinical pathologist Dr Tommaso Fasano, head of the Biochemistry and Laboratory Automation Unit at Arcispedale Santa Maria Nuova Hospital, Reggio Emilia, Italy, has been working with Siemens Healthineers on the manufacturer's new High-Sensitivity Troponin I assay.

His team has found that the new assay offers increased precision and can shorten time points between serial measurements, improving early detection of MI. 'Siemens High-Sensitivity Troponin I has these characteristics and is much better in terms of giving rapid information to the clinician than contemporary assays,' Fasano confirmed.

The assay has been used through his hub laboratory (the Clinical Chemistry and Endocrinology Laboratory), and two bespoke laboratories in the smaller hospitals of Montecchio Emilia and Scandiano, also in the of Reggio Emilia province, since last summer, with evaluation of the assay conducted using the Siemens Atellica IM Analyser and ADVIA Centaur Immunoassay systems. 'We realised that the High-Sensitivity Troponin on both instruments could detect very low levels of troponin, even in patients not having any cardiac symptoms and that is one of the characteristics of high sensitivity assay,' Fasano explained. 'Around 70% of samples having non-detectable troponin with contemporary assays gave us a result that can be reported to clinicians.

Clinical pathologist **Tommaso Fasano MD** heads the Biochemistry and Laboratory Automation Unit at Arcispedale Santa Maria Nuova Hospital, Reggio Emilia, Italy, where has worked since 2010. Earlier, he was a research fellow at the MRC Clinical Research Centre at Imperial College, London, before studying the genetics of lipoprotein metabolism in the Biomedial Sciences department at the University of Modena and Reggio Emilia.

A further benefit was with Emergency Department clinicians able not only to rule-in MI, but also rule-out MI faster, confidently and quicker. 'Our clinicians were used to six-hour protocols to evaluate patients with suspected myocardial infarction,' he said. 'Now, they can shorten this period and we have less requests for troponin because they can safely send patients home after three hours with results compatible with no myocardial infarction.' This, he explained, was aided by the High-Sensitivity Troponin I offering a clearer view on whether a patient has chronic or acute heart damage after MI, or does not have a cardiac issue.

Fasano concedes there were initial communication and education issues with senior clinicians in the change to High-Sensitivity Troponin I use. However, once the evaluation was completed (in terms of giving the same results in values above or below 99 percentile) and its use introduced across all three platforms within the hospital system (serving 500,000 people) acceptance was widespread, particularly due to the positive results.

'An initial fear was that we were going to have an increased number of interventional cardiologic procedures after using the new assay. But, having looked at the literature for the sample, we know there is not an increase in the number of positive troponin. The number of troponin above the 99th percentile is the same more or less between the contemporary assays and the high sensitivity assays.'

An advantage for women

One key advantage has been in the care of women as the assay delivers

tory

Small effort, huge benefit

'Lab tests in geriatric medicine are invaluable, since they offer varied input that helps to ascertain the diseases of the 65+ cohort and thus to determine adequate treatment,' Gutensohn points out. Rather simple lab tests can show asymptomatic diabetes, which could cause severe damage. The individual patient, as well as the healthcare system at large, thus profit from such tests, he emphasises. 'Lab diagnostics is the foundation – with €8.5 billion per year, it only accounts for 2.5 percent of the annual healthcare spend, but affects 60 to 70 percent of all diagnostic and therapy cases.' Since a major share of healthcare resources are used for older people, the diagnostic and treatment options, he believes, should be better aligned with this group.

However, why strive for the early detection of diseases that cannot be cured anyway – such as Alzheimer's? Even in those cases, Gutensohn says, lab tests are beneficial for patients: 'Today lab diagnostics for dementia might be ahead of therapy, but it may well be that in a few years an effective therapy will be available.' Such progress – driven also by high-throughput procedures, multiparametric analyses and big data-based algorithms – is very real, he points out. Moreover, today many diseases might not be curable but nonetheless early detection can increase the quality of life, Gutensohn underlines. 'Take anaemia – the most frequent lab diagnosis in older patients. If detected early on, a few simple measures, such as prescribing iron or vitamins as long as there is no significant further underlying disease, can do a lot of good and enable the patient to live a long and autonomous life.'

Professor Kai Gutensohn is Managing Director and Medical Director of AescuLabor Hamburg as well as Managing Director of Laboratory Group North of amedes GmbH. He has a board degree in laboratory medicine, transfusion medicine, haemostaseology, is health economist and professor at the Medical School of Hamburg University. He is also a member of several medical societies and associations, such as the German Association of Laboratory Medicine (BDL); the Society for Thrombosis and Haemostasis Research (GTH); the German Society for Clinical Chemistry and Laboratory Medicine (DGKL) and the German Society for Haematology and Oncology (DGHO) and the IGLD, Germany's largest group for laboratory medicine.

a sex specific 99th percentile. 'That's important because, in the past, the myocardial damage in women was not well detected and managed because we used to have just one 99th percentile for both male and females.'

Siemen's reports: 'High-Sensitivity Troponin I is the latest addition to Siemens Healthineers' cardiac menu to assist clinicians with diagnosis/treatment of chest pain patients, through the quantitative measurement of cardiac troponin I in serum or plasma. It allows clinicians to measure slight changes between serial troponin I values, giving confidence in patient results at the low end of the assay range.

'Compared to traditional troponin assays, the Siemens Healthineers

Continued on page 11

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Fast detection of drug resistant CPE remains a challenge

Gaining speed in antimicrobial therapy

Early detection and confirmation of carbapenemase-producing enterobacteriaceae (CPE) are essential when choosing the appropriate antimicrobial therapy and to implement infection control measures. Here a leading Spanish microbiologist reviews an arsenal of tools currently available to clinicians.

Resistance to beta-lactam antibiotics in enterobacteriaceae (EBc) is due to one or more of these mechanisms: drug inactivation by hydrolysing enzymes (beta-lactamases), the most common decreased permeability due to down-regulation of porin synthesis, up-regulation of efflux pumps and, less frequently, by target modifications.

In particular, EBc resistant to carbapenemic agents, especially those producing carbapenemases, represent a public health concern, according to David Navarro Ortega, a professor of Microbiology at the Valencia School of Medicine speaking during the 10th Infectious Diseases Day that unfolded in Madrid.

The transmissible carbapenemases are divided into three different classes: class A (serine carbapenemases), class B (metallo-β-lactamases) and class D (OXA carbapenemases, such as OXA-48).

Accurate detection of carbapenemase-producing enterobacteriaceae (CPE) constitutes a major laboratory diagnostic challenge.'Additionally, we cannot reproduce faithfully in vitro what occurs within the infection source,' Navarro said. 'This remains one of our main obstacles right now.'

Differentiation and prediction still take too long

The conventional algorithm to detect and distinguish among these classes of carbapenemases is too slow, it takes up to 48 hours, the microbiologist explained. 'We check if the bacteria show reduced susceptibility to carbapenems in routine inhibitory-based antimicrobial susceptibility testing (AST). If the test is conclusive,' he said, 'it's followed by a confirmatory test, and, optionally, genotypic characterisation.'

David Navarro, fourth from right, among the Haematopoietic Transplant Investigation Group at INCLIVA

Spain follows the EC guidelines on antimicrobial susceptibility testing (EUCAST) to detect resistance mechanisms and specific resistances of clinical and/or epidemiological importance. But the EUCAST meropenem screening criteria have been shown to have difficulties in detecting OXA-48 producers.

A bunch of phenotypic confirmatory tests to detect carbapenemases are available, including combined-disk tests using specific inhibitors, such as EDTA and boronic acid, and the modified Hodge test (MHT).

A number of rapid phenotypic methods to detect carbapenem resistance mediated by carbapenemases, which can be completed in under two hours, have been described, including the detection of carbapenem inactivation by mass spectrometry (MALDI-TOF MS), carbapenem hydrolysis by biochemical (Carba NP test or CarbaNP II TEST), or electrochemical methods (BYG Carba Test). These tests can be run either using cultured bacteria or bacterial pellets derived from clinical specimens, e.g. blood and/or urine.

'The "molecular antibiogram" is an interesting approach to detect EBs resistance to beta-lactam agents, but they predict resistance rather than susceptibility. The latter could be obtained using genotypic, immunologic or mass spectrometry methods could, but they can only be seen as add-on methods to conventional AST testing,' Navarro pointed out.

In the future, he concluded, analysis of bacterial pan-genomic sequences by sophisticated bioinformatic tools obtained by modern deep sequencing methods will provide clinically relevant data, not only on bacterial antibiotics resistance, but also on bacterial spathogenetic traits. (MR)

David Navarro Ortega is Professor of Microbiology in School of Medicine of Valencia and Head of the Microbiology Service at the Clinic University Hospital, Valencia. His research mainly concerns diagnostic, clinical, biological and pathogenesis aspects of herpes virus infections, especially cytomegalovirus in allogeneic stem-cell and solid organ transplant recipients. He has authored/co-authored over 260 publications in intermediate-highly-ranked journals and is a member of the Editorial Board of Diagnostic Microbiology and Infectious Diseases, a member of the ECIL group of the European Bone Marrow Transplantation Society (EBMT) and a regular reviewer for about twenty-five journals.

POCT devices and analysis methods need validation

A coordination office is necessary

Report: Anja Behringer

Point-of-care testing (POCT) is complex and its development continues due to digitisation in healthcare and increasing international partnerships among the healthcare actors.

In a hospital, a number of factors need consideration to fully exploit the potential of bedside testing. POCT instruments and analysis methods must be thoroughly validated and quality assurance processes be in place. Training is crucial but, since this puts an additional burden on staff, procedures should be communicated appropriately.

To manage all these aspects efficiently, close cooperation with the central lab is of utmost importance, says Professor Peter B Luppa, Director of the Central Laboratory at the Institute of Clinical Chemistry and Pathobiochemistry at Klinikum rechts der Isar in Munich's technical university. 'Our POCT working group recommends establishing a coordination office to ensure patient safety in the POCT/central lab interconnection and to guarantee best possible hospital care,' he adds.

The coordinator can contribute significantly to an improvement of quality assurance. But Luppa also takes manufacturers to task: it is their duty to provide instruments that comply with quality assurance standards laid down in the German Medical Association's guidelines on the quality assurance in medical laboratory tests.

In intensive and trauma care there are three lab parameters categories. First, mandatory parameters which directly influence therapy and have to be made available within 60 minutes. These are obvious POCT parameters.

Secondly, there are parameters that are not crucial to avoid an apparent life threatening event but which nevertheless influence diagnosis and/or therapy. According to international standards patients should stay in the A & E department a maximum of four hours. Thus the relevant parameters have to be ascertained within this time period.

Third, there are parameters that do not influence diagnosis and/or therapy but which have to be made available in an emergency to maintain A&E workflow. POCT should be limited to the few crucial parameters and be organised in cooperation with the central lab, which acts as a satellite lab for the emergency room.

Several acute health conditions need immediate laboratory results, e.g. coagulation data in case of a stroke, or cardiac markers when a myocardial infarction is suspected. POCT only rarely provides the same quality of results as the tests done in the central lab, thus there is a trade-off between speed on the one hand and sensitivity and precision on the other.

Moreover, intensive and trauma care departments are open 24/7, which means that at certain times non-critical parameters must be determined with bedside testing.

Going forward, POCT systems need further standardisation in terms of both methods and quality management and the results yielded by POCT should be comparable to lab results.

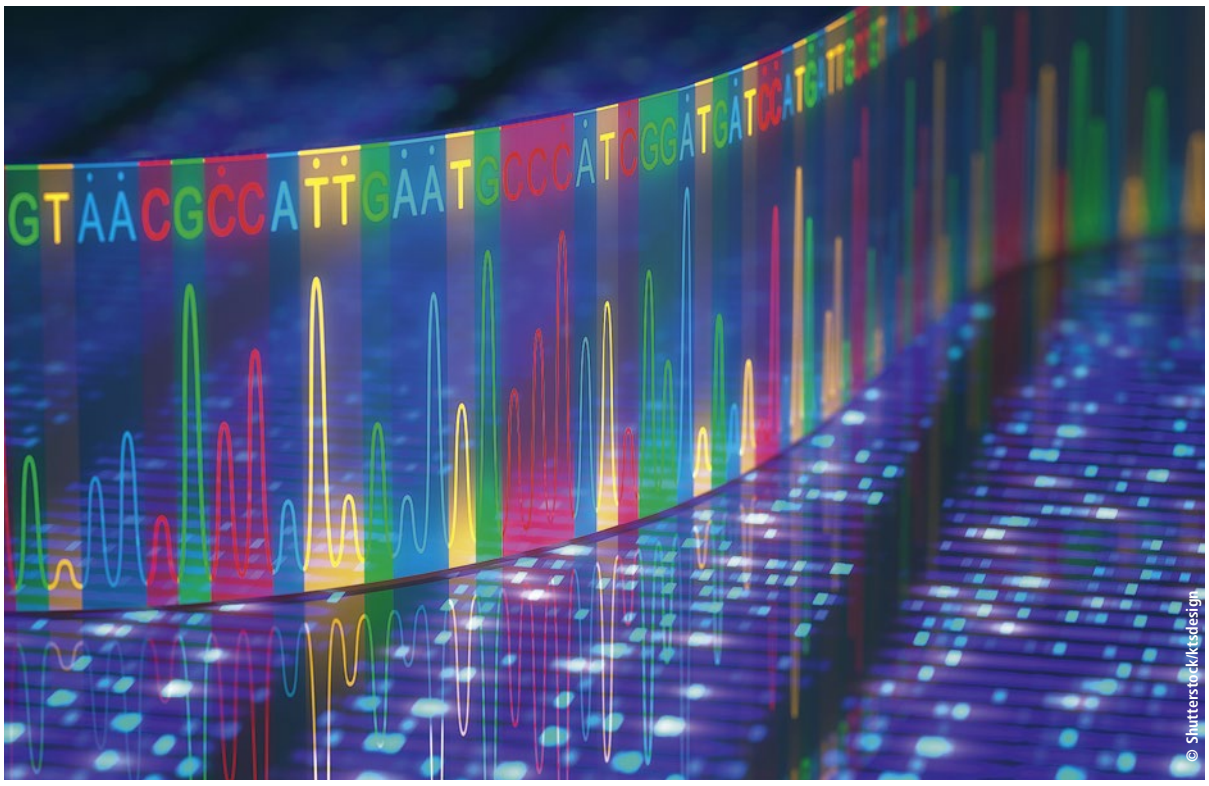
The central lab can play a crucial role in supporting clinical staff and designing methods to compare and correctly interpret POCT and lab results. 'The instruments have to be networked with the POCT coordinator – a fact that has been widely recognised,' Luppa points out.

In the future, he is convinced, 'the enormous potential for the detection of infectious diseases in emerging economies and developing countries will be explored. Detection techniques are revolutionary. Since, in these countries, central labs are few and far between, POCT is the way to go. This is a further reason why POCT quality must be as good as the quality of lab tests.'

Professor Peter B Luppa is head of the Central Laboratory and Blood Bank at the Rechts der Isar Hospital in Munich's Technical University. His main scientific interest lies in the regulation of steroid metabolism and biosensorics, aiming to develop improved analytical-diagnostic procedures for autoimmune diseases. From this, POCT in the hospital developed as a further focus. He has published more than 125 contributions in international journals and is a co-editor of the first German specialist book on point-of-care Testing (now in its 3rd edition).

Administrators should recognise the diagnostics revolution

Sequencing technologies increase patient safety



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Report: Michael Krassnitzer

Gene sequencing has progressed in leaps and bounds over recent years. The process of determining the order of nucleotides in DNA is now faster and more precise. Moreover, both microbial DNA and host DNA can be identified in a patient's infected blood sample, and isolated and sequence d.

'We are facing a technological revolution, but we still struggle with actually implementing these new technologies in healthcare institutions,' observed Professor Jacob Moran-Gilad, MD, MPH, Associate Professor at Ben-Gurion University of the Negev in Israel. At IMED 2018, in Vienna, the microbiologist and public health expert spoke with our European Hospital representative about the gap between the potential of the new generation sequencing methods and the clinical reality – meaning these technologies have not yet arrived – although they could be very useful, for example, for infection control.

'Money,' Moran-Gilad emphasised, 'is not the main problem.' A few years ago, these innovative methods were indeed too expensive for clinical use, but they are increasingly affordable. The problem is rather a methodological one. While generating masses of data with these sequencing-based technologies, there is a lack of standardised methods to analyse the data rapidly and sufficiently to produce clinically actionable information. A lot of promising assays are not yet validated, he pointed out.

The lack of correlation between genomic findings and phenotype is another problem. Especially when it comes to metagenomics, there are limitations. To obtain high-quality genetic material recovered directly from environmental samples for research purposes is very difficult – hence having validated methods to qualify a sample is all the more important. 'We should invest more in quality control, training and standardising of methods to pave the way for integrating these technologies,' Moran-Gilad believes.

Emerging diseases would benefit immensely from the new generation of sequencing methods. State-of-the-art sequencing can provide crucial information on infectious diseases that are either entirely new or have emerged in regions where previously unknown. The pathogen itself or its genetic information can be isolated from a blood sample of an infected person. Depending on the vector, food or water samples can also be tested for the pathogen.

In a next step, the results are compared to epidemiological data, Moran-Gilad said. 'We want to understand the story: Where did this infection come from? Who infected whom?'

In a local outbreak, the regional hospital can most likely handle it. If the outbreak affects a wider area, a reference lab will be involved.

These reference labs, in most cases affiliated to public health agencies, are in charge of diagnostics for certain predefined infections. National reference labs cooperate on an international level. Surveillance networks collect data from different countries or regions.

The European Centre for Disease Prevention and Control (ECDC) operates several such networks. One of the most successful according to Moran-Gilad is the European Legionnaires' Disease Surveillance Network (ELDSNet). Legionella thrives in complex aquatic systems, such as the water infrastructure of large buildings – including hospitals and nursing homes.

This is the vicious circle, says Moran-Gilad: 'My general impression is that hospital administrators don't always acknowledge the ongoing revolution in diagnostics. Sometimes they think microbiologists just want some fancy new toys.' Nothing could be further from the truth: sequencing technologies are important tools to increase patient safety. Moreover, they can drive down costs, as the microbiologist explained. 'Take two infections with the same organism in a certain ward. Usually, such cases are unrelated but that is something you have to prove very quickly. If you cannot exclude a connection, the ward might need to be shut down.'

For hospitals that also perform income-generating procedures the temporary closure of a whole ward obviously can result in a financial disaster.

Microbiologist **Jacob Moran-Gilad MD MPH** is Associate Professor of clinical microbiology at the Department of Health Systems Management, Faculty of Health Sciences, Ben-Gurion University of the Negev, Be'er Sheva, Israel. He is also senior advisor for Public Health Microbiology, Public Health Services, in the Israeli Ministry of Health and Chairperson of the ESCMID Study Group for Genomic and Molecular Diagnostics (ESGMD).

Rapid myocardial infarction verification

Continued from page 9

Atellica IM, ADVIA Centaur, Dimension EXL and Dimension Vista TNIH assays can detect lower levels of troponin and smaller changes to a patient's troponin levels.

'Both Troponin I and Troponin T are released into the circulation at the time of injury following the same release pattern in the system. However, cardiac Troponin I is slightly more differentiated from skeletal Troponin I than cardiac Troponin T is different from skeletal Troponin T.

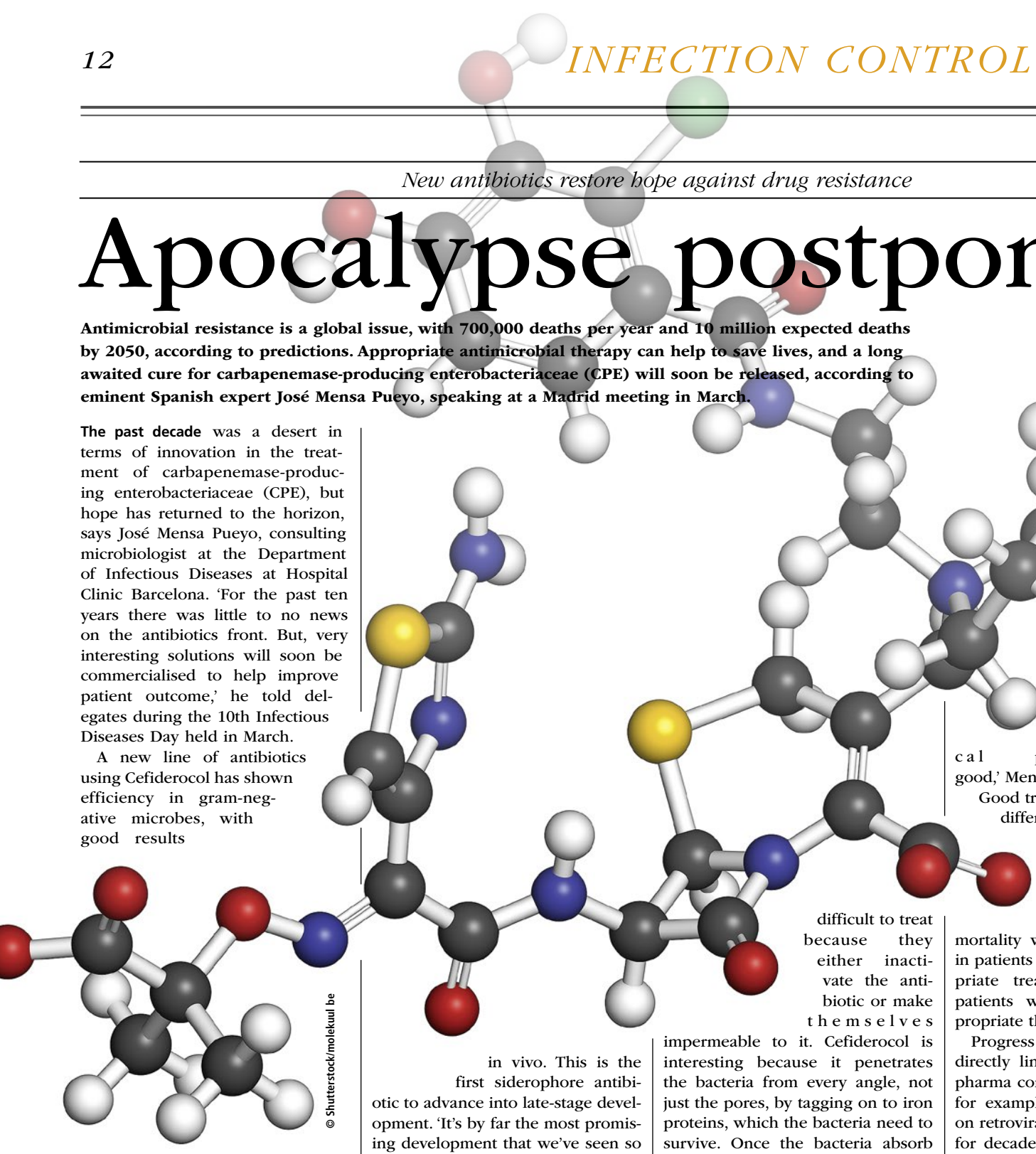
Fasano is delighted with the performance of the Siemens High-Sensitivity Troponin I assay: 'From a laboratory point of view, it's wonderful because it is very precise, you can compare the results day by day, and they are more or less the same.'

A next step is to conduct an economic evaluation on the use of the assays compared to the number of troponins previously requested by the clinicians from the laboratory. 'We think there is less troponin now performed by the laboratory. We would also like to know whether the patients who can go home safely experience a shorter period in the emergency department, which is important for an institution.' (MN)

New antibiotics restore hope against drug resistance

Apocalypse postponed

Antimicrobial resistance is a global issue, with 700,000 deaths per year and 10 million expected deaths by 2050, according to predictions. Appropriate antimicrobial therapy can help to save lives, and a long awaited cure for carbapenemase-producing enterobacteriaceae (CPE) will soon be released, according to eminent Spanish expert José Mensa Pueyo, speaking at a Madrid meeting in March.



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The past decade was a desert in terms of innovation in the treatment of carbapenemase-producing enterobacteriaceae (CPE), but hope has returned to the horizon, says José Mensa Pueyo, consulting microbiologist at the Department of Infectious Diseases at Hospital Clinic Barcelona. 'For the past ten years there was little to no news on the antibiotics front. But, very interesting solutions will soon be commercialised to help improve patient outcome,' he told delegates during the 10th Infectious Diseases Day held in March.

A new line of antibiotics using Cefiderocol has shown efficiency in gram-negative microbes, with good results in vivo. This is the first siderophore antibiotic to advance into late-stage development. 'It's by far the most promising development that we've seen so far,' the expert confirmed. CPEs are difficult to treat because they either inactivate the antibiotic or make themselves impermeable to it. Cefiderocol is interesting because it penetrates the bacteria from every angle, not just the pores, by tagging on to iron proteins, which the bacteria need to survive. Once the bacteria absorb these proteins, they also ingest the antibiotic that will kill them.

'Cefiderocol is a different and unique solution. From a clinical point of view it's very good,' Mensa said.

Good treatment can make all the difference for patient prognosis and is directly linked to mortality. A large study by Gutierrez-Gutierrez B et al. recently showed that mortality was almost twice as low in patients who had received appropriate treatment compared with patients who had received inappropriate therapy (38.5% vs. 60.6%).

Progress in finding new cures is directly linked to investment from pharma companies. AIDS treatment, for example, almost entirely relies on retroviral therapy, which can last for decades. 'AIDS is being treated as a chronic disease for typically 20, 30 years. An antibiotic would kill the disease much more rapidly. But economically it's not that interesting,' the expert pointed out.

Bugs will surely continue to adapt and new types of resistance will emerge in the future; but so will new tools developed by the scientific community and industry. 'We're always at war, it's a constant fight. But this apocalyptic vision, in which everything will end in 2050. and there won't be any drugs to help and we will all die, is completely wrong. Drug resistant bacteria are not that virulent anymore because, if they become permeable, they stop eating and are less active. Resistance tends to occur in fragile patients, not everyone,' he concluded. (MR)

José Mensa Pueyo MD is a specialist in internal medicine and infectious diseases. He is the author of the Guide to Antimicrobial Therapy, a reference guidebook in Spanish, now in its 30th edition (Guía de Terapeutica Antimicrobiana) and available on Amazon. The content is also available through an app and enables quick identification and classification of bacteria.

Neurological complications from (novel) enterovirus infections

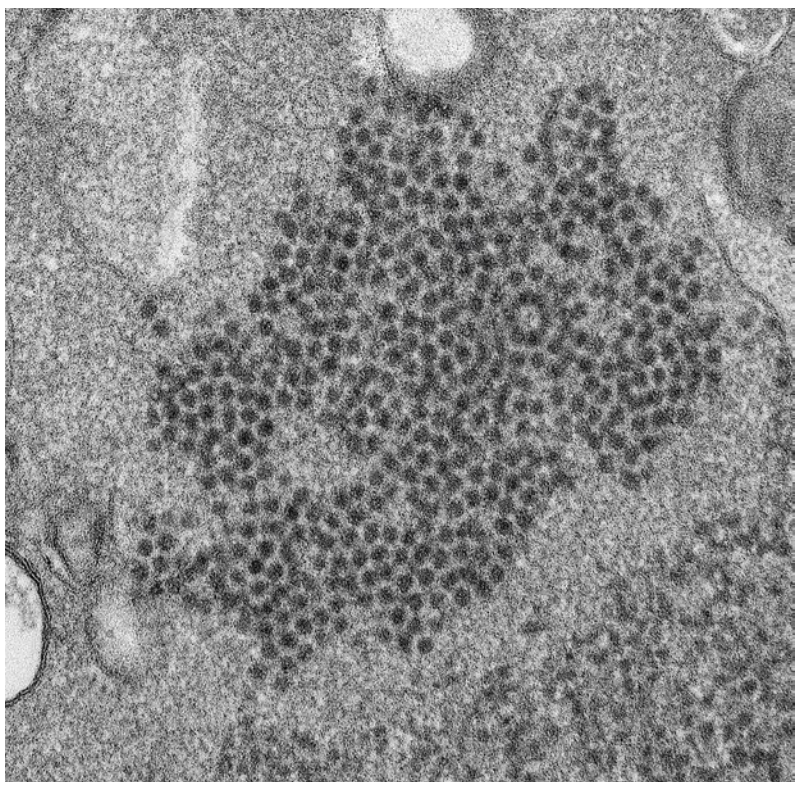
The disease is rare and research scant

Interview: Eva Britsch

Neurological complications due to infections with (novel) enteroviruses are rarely the focus of medical research. Thus, an article published in the German medical journal Der Nervenarzt (published at the Medizinische Hochschule Hanover (MHH) – has created quite a stir. We spoke with one of the authors, Professor Martin Stangel, about current clinical practice in terms of enterovirus.

Enterovirus (EV), Stangel and colleagues point out, is a very common genus of RNA viruses which can cause a broad range of clinical symptoms from unspecific febrile conditions, exanthema and respiratory issues to haemorrhagic conjunctivitis, hand, foot and mouth disease, as well as severe forms of myocarditis and pericarditis, myelitis, meningitis and encephalitis.

The first cases of encephalitis caused by enterovirus were reported in the 1950s. According to Stangel, severe complications, such as encephalitis, were mostly documented in South and Eastern Asia, with none in Europe. Flaccid myelitis was reported mainly in the USA with only isolated occurrences in Europe. Some forms of enterovirus, Stangel explains, have been called the 'new poliovirus', which might fill the gap that polio left.



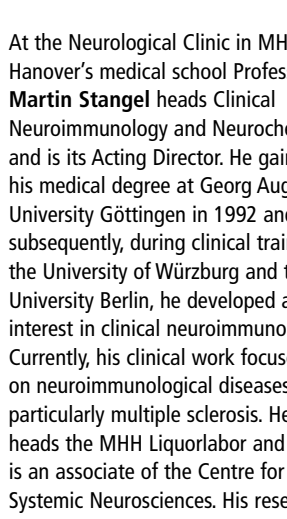
Transmission electron microscopic (TEM) image of numerous, spheroid-shaped, Enterovirus-D68 (EV-D68) virions. CDC/ Cynthia S. Goldsmith, Yiting Zhang

Since the pathologies caused by the viruses and the different case scenarios yield a complex and multifaceted picture, the clinical tests that might identify the virus in clinical routine play a crucial role. However, Stangel emphasises that these tests might generate false negatives and that they differ in terms of sensitivity. 'PCR is the standard but, even here, we see differences as a result of the fact that we are dealing with more than one hundred viruses that are subsumed in the category enterovirus. We have to concede that detection is not always possible.'

As far as therapy is concerned, enterovirus is pretty much terra incognita as Stangel explains: 'On the one hand there is no causal therapy – and thus enormous research potential. On the other, we have to consider that we are dealing with a rare disease.' In other words, the pharmaceutical industry has only limited interest in research, since common diseases such as cancer or hypertension are potentially far more profitable.

Given these facts, is prevention a better approach? Again, reliable data is scarce. The infection path is known, mostly orofecal or via droplets, and certain risk factors seem to be involved, Stangel says: 'Children are the major risk group, particularly regarding encephalitis and meningitis. Socio-economic status is also important, that is: hygiene. Infections tend to be more frequent in summer and autumn, in the tropical regions they are spread evenly over the entire year."

New research results appear to indicate that sooner or later another outbreak of enterovirus infections is very likely.



At the Neurological Clinic in MHH, Hanover's medical school Professor **Martin Stangel** heads Clinical Neuroimmunology and Neurochemistry and is its Acting Director. He gained his medical degree at Georg August University Göttingen in 1992 and subsequently, during clinical training at the University of Würzburg and the Free University Berlin, he developed a keen interest in clinical neuroimmunology. Currently, his clinical work focuses on neuroimmunological diseases, particularly multiple sclerosis. He heads the MHH Liquorlabor and is an associate of the Centre for Systemic Neurosciences. His research publications deal with therapy studies on neuroimmunological diseases and biomarker research in infectious neurological diseases.

The Lean concept in digital pathology

We talked to Dr Annika Blank, Consultant and Lean green belt, about eight-year experience with the concept and optimisation of processes, the implementation of digital pathology and a voice recognition system for patient management.

Interview: Walter Depner

EH: In autumn 2014, Professor Alessandro Lugli reported on the first successful years the Lean concept use in pathology. Originally used in the automobile industry, this was designed to increase effectiveness, improve quality, processes, workflows and customer-orientation and much more. The system also impacts on the premises, staff (e.g. to avoid overtime), and added value. To what extent can you vouch for these improvements eight years on, and what else should be mentioned?

Annika Blank: The biggest and most cost intensive step taken to optimise workflows was the refurbishment of our laboratory, which was completed in 2016. This allowed us to adapt our premises to the workflow defined by the Lean principles. The design of the laboratory with individual work stations is now based on the processing steps for the samples. A very open-plan design has helped to make the path of the samples through the laboratory visible, to cut down on legwork and facilitate flexibility for innovations and communication.

The increase in value-added time has freed up more time resources for other responsibilities. This includes quality control and assurance, staff training and academic obligations, lectures and courses.

Measures implemented so far have been very successful with regards to processing times. Now we are at the point where we need to optimise the defined processes further to avoid stagnation. We are facing two major challenges: actively fighting against 'operational blindness' by constantly scrutinising ourselves and our processes, and redefining processes to make them as simple as possible. Finding simple solutions for problems and ensuring that they can be implemented with ease often poses a great challenge.

Pathology depends on cooperation with colleagues in many different departments/wards internally, as well as with those who send samples from outside the hospital. How has this cooperation developed in the context of Lean?

One of the most important principles of Lean is the focus on the customer. The needs of the patient and of our clinical colleagues are at the centre of our work. We are constantly asking our senders for their opinions and suggestions for improvements through surveys and personal conversations, so that we can adapt our work to this as best possible. We see our task as simplifying the work of individual doctors.

One process where this was implemented successfully was the introduction of standardised reports for malignant tumours. The standardised reports make it easier to achieve a diagnosis as they contain all relevant information and contribute to the completeness of the diagnosis. The structure of the report has led to more clarity and comprehension. Monitoring our processing times makes the release of reports and their availability to those who send in the samples more predictable, which in turn makes it easier to plan the next appointments with patients to discuss the results.

Close cooperation with clinical colleagues is also very important for the quality of the diagnosis as the interpretation of the histological results often depends on the respective clinical context.

What impact has Lean had on the case numbers and staff numbers compared to 2011?

The number of staff members has increased by 7.5% since 2011, and the number of samples received has grown by 40%. The reduction of legwork, waiting times and unnecessary work stages results in more efficient handling, making it possible to process more samples in the same amount of time, without increasing the workload of individual staff members per time unit.

Digitisation of pathology has become an important topic over the last few years. One of the largest institutes in Switzerland, and one of the most important in Europe, must surely be part of this development. What progress have you made in Bern?

At our institute, we integrated digital pathology into the workflows step by step in those areas where we see its implementation creating added value. Digital pathology has been an integral part of our research projects since 2012. Scanned histological sections can be used in many ways. They facilitate access to sections for international cooperation, can be evaluated with the help of image analysis procedures or used as the basis of annotations to develop so-called tissue micro arrays.

Since 2016, we have been using an online platform to exchange information on certain cases with external assessors. Since 2017 this platform has also been used to display sections during case discussions with clinical colleagues and for tumour boards.

Cost-benefit considerations are of essential importance in daily, routine diagnostics. Digital pathology delivers added value for the evaluation of complex parameters, such as the proliferation fraction of tumours based on immunohistochemical markers. We are currently working on the development of robust algorithms for the evaluation of such parameters and will integrate these into diagnostic routine in spring 2019. Something that used to be laboriously counted by hand can now be analysed via automation, as long as it passes the pathologist's plausibility check.

Dr Annika Blank is Consultant at the Institute of Pathology at the University of Bern, Switzerland, where the Lean concept was introduced in 2011. Thus it became one of the first European pathology institutes to do so. Five years have now passed since a Lean audit in 2014, in which the institute scored very well. The period was used to gather considerable experience, to think about further innovations and continued improvements.

Does the Lean concept impact digital pathology, and if so, how?

As digital pathology will soon become part of routine diagnostics, it is integrated into our workflow of laboratory processes and must adhere to the Lean principles to keep up with the pace of our case processing. Lean principles can not only be implemented in the design of workflows but will also be used for the appropriate utilisation of our resources and for quality control, particularly for quality of scans.

The institute's annual report mentions that the introduction of voice recognition for the patient management system is an important component. How far have you progressed in this field?

The introduction of voice recognition in diagnostic routine was one of our main objectives for 2019, on a medical level. It was implemented in March and has proved itself for the drafting of short reports of findings. Voice recognition will continue to be adapted to our needs and requirements throughout the year until it is also suitable for complex reports of findings.

The future holds workforce challenges

Pathologists will hold a pivotal role

Amid ever-growing demand for services, significant challenges face the pathology workforce in the years ahead but – there are also good opportunities.

With advances in technology and the advent of artificial intelligence as a decision-making support tool, Professor Jo Martin, President Royal College of Pathologists (RCPath) in the UK, believes there remain opportunities for pathology to play a pivotal role in a new era of healthcare delivery. After the latest National Health Service (NHS) long-term plan unveiled late last year, Martin pointed out that pathology can help address some of its issues and goals.

Her views were outlined in her presentation 'The workforce pressures facing pathology and what are the potential solutions' during the Frontiers in Laboratory Medicine (FiLM) conference in Birmingham, England, at the end of January, where workforce pressures and plans to address the challenges were a key aspect. Speaking with European Hospital ahead of her presentation, the professor detailed the current workforce position within the UK, referencing new RCPath data gathered from clinical biochemistry and histopathology colleagues, and also suggesting how the sector can support the National Health Service future more broadly.

'Some of the NHS long-term plan objectives are only possible with the support of the pathology community and with investment and support for our workforce.'

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Headline elements in the NHS 10-year plan include genetic tests for all children with cancer; putting the health service on a digital first footing; giving patients personal budgets to fund their own choice of treatment; cutting back on bureaucracy; increasing spending on mental health; a greater focus on prevention, genetics and more out-of-hospital care.

One area where pathology has a role is also around the commitment in the plan to out-patient re-design and reducing the number of unnecessary appointments by up to a third (in 2017-18, there were 119.4 million out-patient appointments, of which 93.5 million were attended), perhaps moving to a condition where a significant amount of patient follow-ups can be run from and by colleagues in pathology. 'With good algorithms and systems designed by our clinical scientists and medics, we have models that would be very helpful, and take the pressure off our primary care and acute colleagues,' Martin added.

Other areas of the plan where pathology is essential are in rapid diagnostic centres, early diagnosis of cancer, and around mental health and prevention. 'It's about ensuring we have enough people in training, that people want to stay in work and enjoy what they are doing,' she said. 'Recruitment and retention are absolutely key, along with a commitment for continuing professional development, and improved interoperability with more robust IT to make the pathologists' work easier.'

RCPath has conducted workforce surveys among clinical biochemistry and histopathology disciplines, with

Continued on page 15

Professor Jo Martin is President of the Royal College of Pathologists and a practicing histopathologist, specialising in renal pathology and gastro-intestinal neuro-muscular disease at the Royal London Hospital. She also directs Academic Health Sciences, Barts Health NHS Trust, and is Professor of Pathology at Queen Mary University of London. Her research interests lie in gastro-intestinal and neuro-muscular disease of the gut as well as drug development.

Digital pathology and AI push for integration with radiology

Multiple viewing improves consultation

Pathology is embracing digitisation just as radiology did over 20 years ago and both specialties are looking at new ways to integrate each other in their workflows. AI could fuel this sparkling alliance, giving it further means to improve cancer treatment, a panel of experts from both disciplines told delegates at ECR 2019.

Report: Mélisande Rouger

Radiologists and pathologists both work with images and have very similar workflows, according to Lluis Donoso Bach, Director of the Diagnostic Imaging Department at Hospital Clínic of Barcelona.

'We both perform image acquisition, visualisation and then write a report. Digital images can now also be viewed by pathologists. Exploring new cooperation paths is a natural evolution,' Bach explained.

Benefits that can emerge from increased cooperation between the two disciplines include immediate access to data needed in clinical routine, which can become handy in multidisciplinary tumour boards and for remote physicians, and avoid the risk of breaking, losing or wrongly sorting glass slides.

For the past eight years, Paul J van Diest, head of the Pathology Department at the University Medical Centre (UMCU) in Utrecht, has successfully worked to digitally transform his department. His team now has a complete digital pathology workflow, which considerably improves efficacy, he said. 'There is no more case assembly in the lab, but quicker diagnostics and preparation of multidisciplinary meetings. Searching slides for a big oncology meeting would take a full day. Today, there's no more of that; everything is on our screen. We hardly ever go to the archive anymore.'

Working in a digital environment also enables annotations to be taken, notably 3-D annotations, which is much easier and safer than writing on slides. 'We used to scribble with a pen on slides. Now we do annotations like radiologists have been doing for decades. It's so much easier, for example when taking measurements to the resection margins. In prostate biopsy, we have to estimate the volume that's been taken up by the tumour. How do you do this is in a non-digital way?' he asked. 'It's just completely not reproducible and inaccurate.'

Probably the best selling point of digital pathology is that it improves patient safety. The list of benefits is long: easier and more accurate measurements and counting; better overview of tissue present; the possibility to flag missing slides, track viewing and automatically link images to reporting and the LMS. 'This means there's no more wrong report to the wrong patient - no more mixing up of slides,' van Diest said.

Switching to digital also means multiple observer viewing, which improves workflow and consultation. Revision between labs can also be done on the same day and pathologists can work paperless and with better ergonomics. Teaching is also much easier, since students like digital teaching more than slides.

Van Diest is now working on integrating images into the electronic patient record, another step that would improve workflow.

Integration with radiology makes more and more sense for pathologists and radiologists to improve the quality of their services and workflows. Digital pathology and AI are strongly pushing in that direction, van Diest argued.

'There is definitely a case for inte-

In 1996, **Professor Paul J van Diest** gained his medical doctorate followed by Board certification in Pathology at VU University medical centre (VUMC) in Amsterdam, where he was then Consultant Pathologist in the Pathology Department. In 1999 he became Associate Professor and, in 2001, full Professor. He moved to head the Pathology Department at the University Medical Centre (UMCU) in Utrecht in 2003. He is also Adjunct Professor of Oncology at the Sidney Kimmel Oncology Centre at Johns Hopkins, Baltimore, USA, and visiting professor at the University of Siena, in Italy. He is on the editorial board of 23 international journals, has published around 700 papers in peer-reviewed journals; personally supervised about 70 PhD theses, and been active as secretary and president of various international societies.

The new era of digital pathology

Disease processes by pixel an

As reporting workload for pathology departments continues to rise rapidly, artificial Intelligence solutions are set to play an increasing role in daily practice.

In many pathology departments the annual number of cases has risen by around 2-4% but the slides produced has doubled in the last decade. Histopathologist Professor David Snead identified this phenomenon within his own centre in the United Kingdom and outlined a similar scenario during his presentation – 'Disease processes by pixel analysis: the new era of digital pathology' – at the Digital Pathology and Artificial Intelligence Congress held in London in December. 'I see this as the future of digital pathology,' he said, when he outlined how deep learning and artificial intelligence (AI) is on the way to revolutionising pathology practice.

'As a practising histopathologist, the key reporting workload is going up; we are producing double the numbers of slides from the same number of cases and we need help as this avalanche of work continues. We need to prepare for having the pathology workload aided by computer, with image analysis taken over by the deep learning approach.'

Digital whole slide imaging (WSI) is allowing pathologists to use computer workstations for routine diagnostic work, facilitating the adoption of algorithms to assist the diagnostic process. This, he said, has coincided with development of convoluted neural networks and machine learning, delivering remarkable advances in AI; a new era for histopathology beckons he believes, in which 'widespread adoption of algorithms to improve and standardise the reporting of diagnostic samples is anticipated.'

His presentation highlighted AI development applied to digital pathology to date, and referred to some recent studies for insights into likely developments in this field.

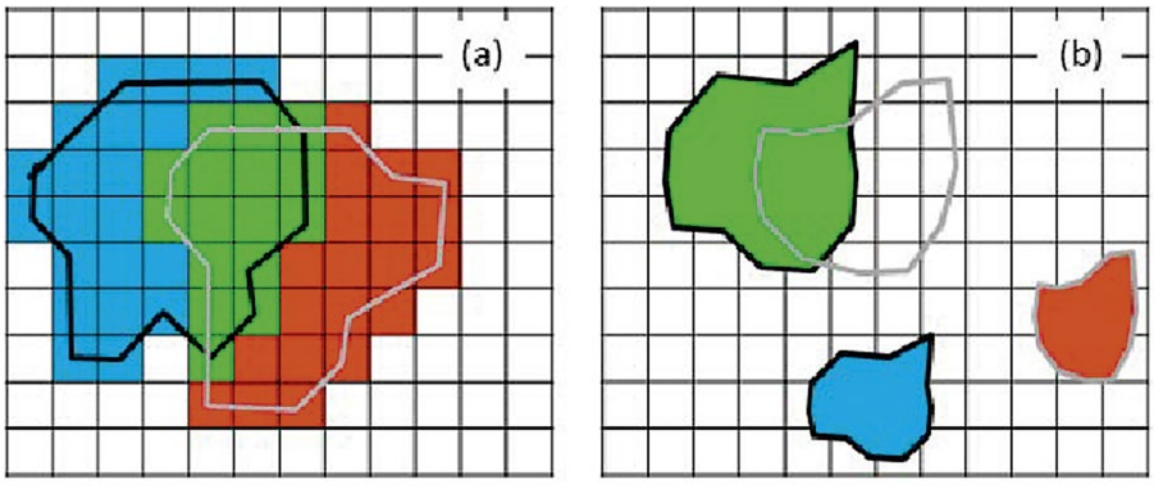
Snead, Consultant Histopathologist and Clinical Service Lead for Coventry and Warwickshire Pathology Services, outlined the benefits and scope of AI in cellular pathology in terms of automation; biomarker assessment; cancer detection; cancer grading; prognostic and predictive tools, and research. 'Some aspects of the workload, particularly the screening of slides for regions of interest, will become automated, with widespread adoption of algorithms scanning slides ahead of the pathologists first review, enabling direction of attention to areas of importance,' he predicted.

Breast cancer already features highly in the literature predominantly for image analysis of biomarkers, Snead added, and pointed to an example of Her2 scanning in a man versus machine context, in which the machine with digital image analysis outperformed manual biomarkers in breast cancer assessment.

The Camelyon 16 challenge showed that the best algorithms perform at least as well as a pathologist, he added. Importantly, Snead noted that, when pathologists were given unlimited time to analyse an image, they performed well. However when placed in a scenario of the time-constrained real-world environment of a clinical setting, they performed worse than the computer, highlighting the benefits of the pathologist and AI working in tandem in disease processes by pixel analysis.

'When you combine the pathologist and the algorithm you get better overall results. So much for improving what pathologists already deliver – what is it that AI can do that the pathologist can't? These are areas in which we expect the next major advances to be made.'

An important area, said Snead pointed out, is analysis of the interaction between tumour cells and their microenvironment. With surgically resected lung cancer the patient wants to know how they are going to do, he explained, while the clinician wants to know if they need further treatment. AI has ben-



Lightning (black) and Cb-TRAM (grey) objects. (a) Pixel-based analysis: the pixels covered by the lightning and the Cb-TRAM objects are counted. (b) Object-based analysis: the lightning and the Cb-TRAM objects are counted. Green are the hits, blue the misses, and red the false alarms (adapted from Forster and Tafferner, 2012).

© Image available from: https://www.researchgate.net/figure/Lightning-black-and-Cb-TRAM-grey-objects-a-Pixel-based-analysis-the-pixels_fig3_258748304 [accessed 11 Apr, 2019]

Lluís Donoso-Bach gained his medical degree from the School of Medicine of the Autonomous University of Barcelona in 1981. He completed his residency in radiology at the Hospital de Sant Pau in Barcelona, in 1992, and in that year was appointed Chairman of the Radiology Department at the UDIAT Diagnostic Centre. In 1998 he became its Executive Director. Since 2006 he has led the Diagnostic Imaging Department at the Hospital Clínic of Barcelona and been Professor of Radiology at the University of Barcelona.

gration of image analysis and deep learning. During diagnostic work, we often use completely subjective features to make a diagnosis. For example, we diagnose cancer when we see, within the tissue, big nuclei, variation of shape or size between the nuclei, or when the chromatic pattern of nuclei are irregular, etc. But these are all subjective, and we're easily tricked in our visual system in assessing size, so we're going to measure it,' he explained.

Ideally pathologists could use AI and image analysis in several applications, e.g. mitoses, nuclear area, degree of tubule formation and metastases finder, 'a tedious task, where we might miss things.'

Integration would also make sense in immune infiltrate quantification; IHC membrane scoring and positive nuclei scoring; and tumour vs. stroma quantification, which is becoming quite popular in breast and colon cancer.

Mitoses counting in breast cancer usually takes pathologists 10-15 minutes. An AI algorithm could be used as a pre-screener that finds candidate mitoses to expedite the process. 'We could click on the ones we like and don't like and end up with a number of mitoses for a different area, of typically two square millimetre.'

In nuclear segmentation in breast cancer, pathologists could segment the nuclei with image analysis algorithms without having to estimate in a subjective way.

AI algorithms are also particularly helpful in immune infiltrate quantification, an important prognostic feature that proves more difficult to assess in colon cancer than in breast. 'You have more tissues, muscle, fat, etc.,' he said, 'and you only need to count a number of infiltrating inflammatory cells in a tumour area, so all areas must be recognised,'

Finding metastases in breast cancer is a tedious task in which pathologists typically have to put under and look at 50 slides, a process that can take up to 20 minutes. The missed rate is high. Van Diest and colleagues, who recently revised the original material from a big breast study, found that pathologists missed 23% of central node pathologies. 'We need something to do a better job. AI did get better results than very experienced pathologists at detecting lymph node metastasis in breast cancer,' he pointed out.

The problem remains that, so far, very few AI algorithms have been implemented in clinical cases. 'We are not there yet.' Van Diest concluded. 'Workflow needs to be completely integrated and we need fully integrated image analysis, but we need to do this step by step.'

nalysis

efits in tumour cell morphometrics to predict survival in lung adenocarcinoma. Similar work is being conducted for prostate cancer and breast carcinoma, he said.

In several tests/challenges Snead acknowledged how the computer is at least as good as the pathologist and sometimes probably better, e.g. to predict which lung cancers harbour mutations in the EGFR gene.

The UK government is funding five centres to advance AI in image diagnostics. Digital pathology is central to three of these centres including the Coventry PathLAKE centre, of which Snead is director. This initiative is designed to connect the UK's excellence in AI, its strength in real world NHS clinical data and the innovative SME start biotech sector, to encourage innovative ideas and solutions. However, he warned, 'Such solutions will only get into the clinic if we can validate these tools and get them approved through our regulatory framework.'

He remains confident that this can be achieved by working with regulators and helping to align processes with the FDA, and across the EU.

Digital image analytics is moving into practice, he said, but there are many challenges that remain including interoperability across platforms, variability of sections and of staining, quality assurance of performance, implementation controls, and accreditation.

A key advance would be for the elements to come together to provide algorithms that are truly interoperable and perform on different platforms, he said. 'Digital pathology is progressing without these algorithms at the moment, but adoption will be speeded up when really useful algorithms come along.' (MN)

In 1997, NHS consultant pathologist **Professor David Snead** works at the University Hospital of Coventry and Warwickshire, where he is clinical lead for Cellular Pathology at Coventry and Warwickshire Pathology Services. Having led the implementation of digital pathology at the centre, his main research interests lie in extending the capability of digital pathology for routine diagnostic use and the advancement and deployment of computer assisted diagnostic algorithms.

TMAs could be a vital screening tool for radiology

Infusing tissue microarrays with new life

Report: Mark Nicholls

The advent of digital pathology is helping to address some of the challenges surrounding tissue microarrays as they are integrated into the digital workflow, in some ways giving them 'a new lease of life', according to Professor Inti Zlobec, who spoke at the Digital Pathology and AI Congress in London last December. As Head of the Translational Research Unit at the Institute of Pathology, University of Bern, she pointed out the challenges surrounding next-generation Tissue Microarray (ngTMA) and explored the benefits of coupling with digital pathology in translational research.

A long work history with tissue microarrays indicates that digital pathology is now 'vital to the whole process' of how TMAs are constructed. Reflecting on the early days of TMAs from 1998 and the combination of different spots on one block, Zlobec said the idea uses less resources and material and, by adding associated pathological data, a research tool can be created that can last 5-10 years.

It was clear for some time that TMAs might be a valuable screening tool, and her team, which has a focus on colorectal cancer, was interested in tumour budding but the challenge was how to get budding on a TMA.

'One solution was to incorporate digital pathology into the microarray workflow,' she said. 'The digital slide could be used to annotate exactly the region or multiple regions you wanted. By increasing the resolution, you could really see what you were putting on the TMAs.'

The next-generation Tissue Microarray approach, which utilises slide scanning and digital annotation as a basis for TMA construction, has been used in her lab since 2012. 'The beauty of that is that you have fully annotated – and documented – spots and images. There was also the ability for every single spot to have clinical and pathological information and the clinical outcome for every single patient.'

Her Bern group created 720 TMA blocks with about 150,000 punches thumped physically into the blocks.

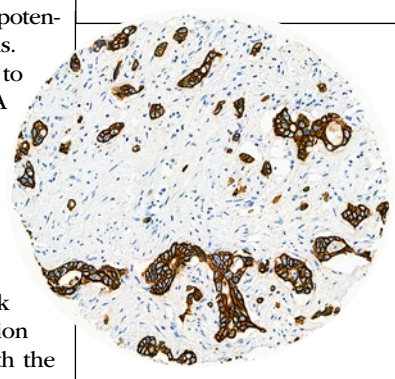
While colorectal cancer was the main focus – about 30% of the blocks – the team also created tissue blocks for lung, pancreas, oesophagus, prostate and other areas.

Ultimately the process led to more than one million images in the TMA archive from different tumour entities (after TMA cutting and staining) and all with the associated pathological annotation, histological information and clinical outcome… and potentially available for image analysis.

'Now the problem is how to manage that number of TMA slides,' she said. 'A solution is with machine learning tools and having the TMA spots linked back to patients, whole slide images, annotative information and image analysis results, though this is still work in progress.' Another question Zlobec posed was whether, with the ever-advancing technology, TMAs are still relevant and, she noted, the number of annual publications on the subject had plateaued in recent years at about 600. The original aim of TMAs of screening and resource efficiency, she said, was still relevant and, they can be used to study heterogeneity, biomarkers, and to capture the tumour environment. More recently, the Bern group has developed a tool (Scorenado) that provides an intermediate solution to image analysis, facilitating user-friendly visual assessment on digital slides. Today, TMAs are a resource in the machine learning era for classification or prognosis and prediction for patient outcomes and also for translation into clinics.

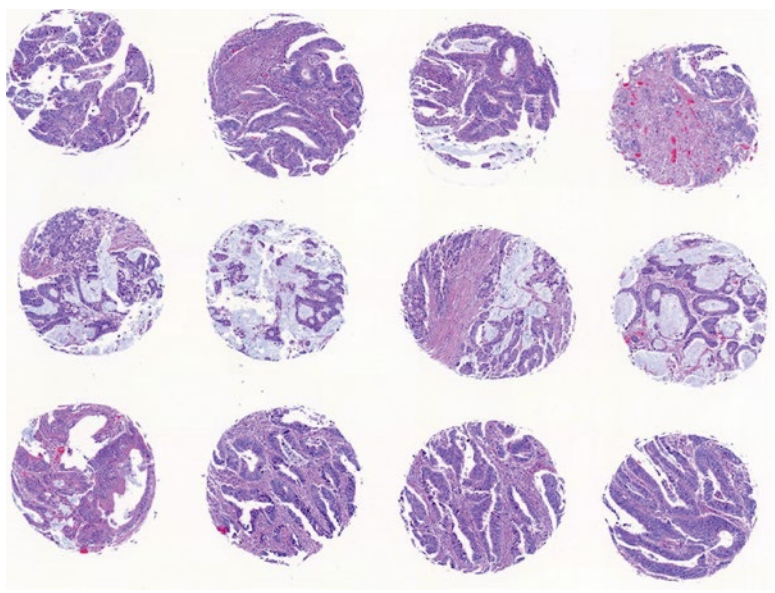
'They also combine technology with molecular applications – we can take the punch we put on a TMA and then put it into a tube to do the sequencing, giving us the kind of documentation we really need,' Zlobec explained, also pointing out that digital pathology also can complement mass spectrometry, identifying and validating new biomarkers. As digital pathology evolves, its added value to TMA use becomes clear. It improves, she pointed out, the quality of biomarker studies with precise ngTMAs that quickly capture ROIs; uses digital image analysis; improves documentation; aids biobanking and the accreditation process; it also offers high quality pathology standard annotation of images, and can be combined with molecular applications. Additionally, using the image as a biomarker adds a huge wealth of morphology information.

Professor Inti Zlobec heads the Translational Research Unit at the Institute of Pathology, University of Bern. Her interests lie in interdisciplinary translational research to improve the clinical management of patients with colorectal cancer and in histomorphological biomarkers as prognostic and predictive features of tumour response to therapies.



Single spot from a next-generation tissue microarray of colorectal cancer stained with pan-cytokeratin

Snapshot of an H&E stained next-generation Tissue Microarray



Pathologists will hold a pivotal role

Continued from page 13

the haematology survey in progress. Data from the clinical biochemistry survey is currently being analysed with results imminent, but findings from the histopathology report have been described by Martin as 'gruesome'. 'The survey showed that 97% of laboratories do not have enough histopathologists, and it's going to get worse. 2021, we are expecting somewhere around 25-28% gap in the histopathology workforce.

'RCPath is making the case for more pathologists, with support from a range of charities and other organisations, in its efforts to get investment in the laboratory and diagnostic workforce. This data means we can show exactly what the issue is.'

Pressure has grown in recent years because of increased workload, not enough trainees, with a lower profile in medical schools and limited opportunities to meet pathologists. Additionally, an ageing workforce exists with a quarter of histopathologists aged 55 years or over, as well as the risks of stressed practitioners opting for early retirement.

'We need to de-stress the system to take the heat off current people so that they are prepared to stay,' Martin emphasized. Digital pathology and AI support will help, she believes. With high levels of pathology expertise in the NHS, she remains optimistic about the future for pathology with the various disciplines poised to play a pivotal within future diagnosis and care delivery. (MN)

Superlative future assistance

As a member of the European Congress of Radiology (ECR) planning committee Professor Elmar Kotter suffered no serious challenge in pinpointing subject matter for the IT sessions. More than 300 submissions were received on artificial intelligence (AI). From the presentations, Kotter, Professor of Radiology and Senior Consultant at the Clinic for Diagnostic and Interventional Radiology, at the University Hospital Freiburg, concluded that AI indeed presents opportunities to improve workflow.

AI applications to detect lesions or fractures in various contexts are now almost standard. An artificial neural network is trained using an annotated data set. The underlying technology is established and mostly independent of the specific localisation. 'Image recognition is obviously an important and invaluable application, but the range for the utilisation of AI is much broader than that,' Kotter points out.

Needs-based resource planning

'By comparison, I believe that using AI to predict increased patient numbers, for instance, is much more innovative and exciting.' Once this is established in hospital routine, it could be used in many areas. 'It could develop into a helpful tool to improve needs-based utilisation of resources without increasing pressure on staff or equipment,' Kotter believes. The main benefit of AI he sees is primarily in process optimisation - not only in radiology but across an entire hospital. However, he believes a long time will pass before AI can deliver diagnoses autonomously.

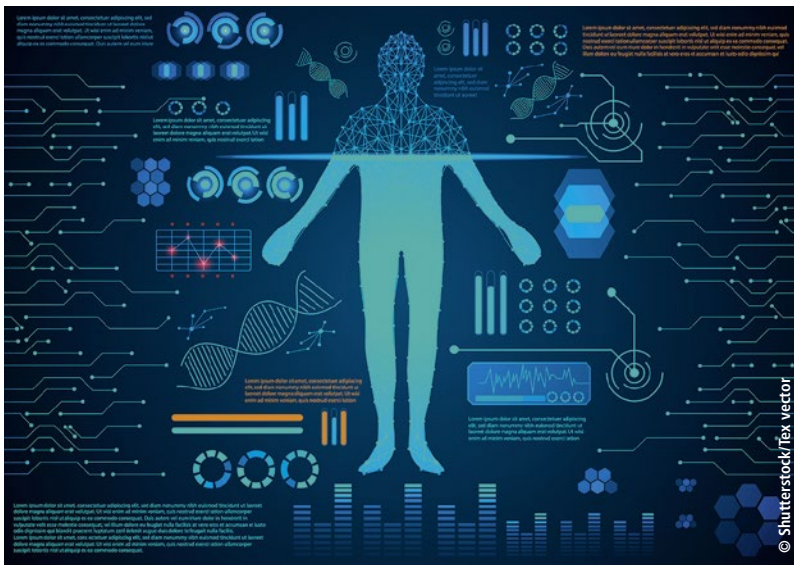
Optimisation of exam protocols

A fundamental problem that affects the optimisation of examination protocols is the inconsistency of exam descriptions, beginning with a request for a specific examination (termed 'order entry'). Because the exam description is later transferred into the radiology information system, the description must be identical in both systems – the only way to ensure that the procedure requested is clearly defined and that the correct protocol is retrieved on the equipment used.

The situation is aggravated because hospitals use devices from many different manufacturers that use their own descriptions. Currently, to help visualise this clearly, extensive manual mapping is being carried out to align the different descriptions in the systems. 'To give you an example,' says Kotter, 'here in Freiburg we work with 13,000 different examination descriptions.'

The dose management system at the end of the process must merge the different descriptions in identical categories before the data can be analysed – e.g. which dose was used, which outliers were observed etc. The approach of an AI-controlled process could be to automatically recognise what was examined based on images, for example, whether a procedure was a cardio CT or a standard abdominal exam. 'This AI-controlled process could really help us to avoid inconsistent descriptions and their manual alignment,' Kotter reasons.

An ideal relationship between image quality and dose



A further area of AI application is image quality recognition. Generally the higher the dose, the better the image. However, the challenge is to find the lowest possible dose that can be used to produce the best possible image and therefore the best diagnosis.

This needs the automatic evaluation of image quality for any given problem for each individual examination, which can then be correlated with the dose used. 'This is a typical case for AI,' says Kotter –unfortunately no one is working on this yet.

Conquering the information onslaught

Certain problems can only be analysed with the help of very high information density. At some point, humans reach their limits, with the evaluation of multiparametric MRI data for instance, and certainly when genomics data is included in the diagnostic process. 'In my view,' Kotter is convinced, 'AI-controlled processes are predestined to conquer these enormous amounts of data.'

The hospital discharge letter provide another example. Depending on individual patients, it is not unusual to see twenty pages of discharge documentation – a real time problem for radiologists.

'It would be extremely helpful if artificial intelligence could extract relevant patient data in an intelligent way, supplement it with other information (such as pathology data), and then evaluate and present it intelligently,' Kotter suggests, concluding: 'I imagine AI as a kind of superlative, executive assistant.'

(DZ)

Dr Elmar Kotter studied Medicine and Computer Science at University of Montpellier (France) and Université René Descartes in Paris (France). Since 2003, Dr Kotter is vice chairman of the Department of Radiology, University Hospital Freiburg and Associate Professor of Radiology at Freiburg University since 2008. Dr. Kotter served as chair of the information technology working group of the 'Deutsche Röntgengesellschaft' (German Society of Radiology) from 2006 to 2015. He is also vice-president of the European Society of Medical Imaging Informatics (EuSoMII).

Huge data taxes human brians

Hopes for hybrid imaging lie in AI

During a European Society of Hybrid, Molecular and Translational Imaging (ESHI) session at ECR 2019, three speakers discussed the role of artificial intelligence (AI) in hybrid imaging.

While AI and machine learning is supporting clinicians using hybrid techniques such as PET/CT, MR/PET, or ultrasound and CT, challenges remain in 'training the machines' to add value to radiologists' and image analyses.

To do that, large amounts of data are needed but, to enable proper data mining and machine learning, **Osman Ratib**, professor at the University of Geneva and Chair of the Division of Medical Imaging at Riviera-Chablais Hospital in Vevey, Switzerland believes the medical world still falls short in providing the necessary amount of data in a well-organised and curated way. He pointed to the need for open research data in an era where medical practice has changed from generic to personalised, from empirical to evidence-based.

Five Big Data challenges were itemised: no common vocabulary in radiologists' reports; a lack of annotation and mark-up standard; the need for measurement uniformity with multiple image interpretation platforms; the need for public data sets and to create a shared imaging archive; and an ongoing disconnect between DICOM and HL7.

'We need Big Data archives but it's difficult to get different centres to contribute to that,' Ratib pointed out.

He also dismissed fears that AI could make radiologists obsolete one day. The discipline needs to embrace the tools as 'aids and enhancements to human intelligence' and to help alleviate. the global shortage of radiologists by enhancing productivity; improving diagnostic accuracy and delivering fewer misdiagnoses.

Educating the machines remains a leading challenge. The aim is to transfer human knowledge without having to put an algorithm into the machine, Ratib explained, because machines learn to perform image analysis in a 'supervised' and 'unsupervised' way.

'The unsupervised part is when it gets scary because we do not know quite what is in the black box and what the machine is thinking. The challenge of the unsupervised element is trying to work out what we want the machine to do that we are not doing today.'

Imaging biomarkers are a major component of Big Data driven medical knowledge and decision-making, the professor concluded and predicted that structured databases of diagnostic imaging will play a major role in the era of personalised medicine with new radiomics features able to provide a significant advance in computer aided diagnosis.

Artificial intelligence, radiomics and holomics

Dr Irène Buvat, from the Service Hospitalier Frederic Joliot in Orsay, France, focused on the role of AI and holomics in predicting what is true from hybrid imaging and non-imaging data.

Whilst radiomics is about designing predictive models from image-derived features, using AI to select the best combination of features and create a predictive model, holomics takes this to a new level and is defined as 'the gathering of genomic, radiomic, proteomic, clinical, immunohistochemical and many more data, and their integration in predictive or prognostic models'.

Buvat: 'AI is needed because the human mind cannot comprehend this amount of data, but radiomics in itself is not likely to be sufficient; we should also use clinical data, genetic data, pathological slides and blood samples in addition to imaging.'

Although hybrid modalities can deliver the data, there are challenges to radiomics and holomics on model design and interpretation and how a centre applies its model to data from other centres.

Radiomics plus prediction modelling

Dr Antoine Leimgruber, head of Nuclear Medicine and Oncology at Riviera-Chablais Hospital in Vevey, Switzerland, discussed 'radiomics+: prediction modelling using convergent data'.

He maintained that radiologists have to adapt to be part of a rapidly moving medical arena, describing artificial intelligence as 'a wonderful asset' for the medical imaging and hybrid imaging community from the perspective of personalised medicine. Radiologists need to harness that to become relevant players in this new field rather than being side-lined.

'Medical fields are evolving quickly and the medical imaging community needs to respond,' he underlined. 'There are new challenges to imagery, with diagnostic tests such as liquid biopsy, but we can respond by building our expertise; we need to be relevant and give relevant advice to clinicians but also by developing techniques.

Through radiomics, radiologists can not only increase the amount of data provided to clinicians but can also 'join the data stream'.

(MN)

Osman Ratib, professor at the University of Geneva and Chair of the Division of Medical Imaging at Riviera-Chablais Hospital in Vevey, Switzerland

Dr Antoine Leimgruber, head of Nuclear Medicine and Oncology at Riviera-Chablais Hospital in Vevey, Switzerland

Dr Irène Buvat, Service Hospitalier Frederic Joliot in Orsay, France

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Effective diagnosis and care needs a multi-disciplinary team

A Belgian prostate unit at work

Pathologists, radiologists, urologists and radiotherapy specialists sit at the core of the treatment pathway for the patient, working together as a cohesive unit.

In an innovative 2019 ECR session in Vienna, the prostate unit from Ghent University Hospital in Belgium outlined how the team works to deliver the best clinical outcome for patients.

Session chair Professor Geert M Villeirs of Ghent University Hospital – and President of the Belgian Society of Radiology - set the scene from the moment a patient is informed that Prostate-Specific Antigen (PSA) is elevated.

'Our task,' he said, 'is to find the reason for it, either via non-invasive or invasive techniques. Once we know the pathologies, we have to treat – either surgically or non-surgically.

'All these building blocks come together as the prostate unit – the radiologist, pathologist, urologist and radiation oncologist – to discuss the patient.'

Radiologist Dr Pieter De Visschere, from the Department of Radiology and Nuclear Medicine, outlined the role of imaging modalities in the process and their importance to the multi-disciplinary prostate team.

Transrectal ultrasound in cases of elevated PSA or abnormal rectal examination, he said, was a useful modality and ideal in biopsy to confirm the needle is in the right place in the prostate.

However, he noted that prostate cancer is much more visible on MRI than ultrasound and that most prostate cancer (70%) is in the peripheral zone.

The Ghent team use multiparametric MRI (mp-MRI), combining elements of diffusion-weighted imaging (DWI), Dynamic Contrast Enhanced imaging (DCE) and spectroscopy.

'In terms of accuracy of prostate cancer detection, mp-MRI is accurate for larger tumours but frequently misses small or low-grade tumours,' De Visschere explained. 'However, this is not as important as it used to be as the diagnosis of prostate cancer and the treatment has changed.'

In the past, following PSA elevation and biopsy, all prostate cancers were treated but that led to overdiagnosis and over treatment. 'Currently, the aggressiveness of the cancer is considered,' he pointed out. 'With a clinically significant prostate, cancer treatment can be surgery, radiation therapy and hormonal therapy. With a clinically insignificant prostate cancer there would be active surveillance and postponing treatment but with close follow up and treatment would only start in a case of evolution to clinically significant prostate cancer.

'In addition to diagnosis, we can use MRI for local staging, detection of local recurrence and recurrence after radiation therapy.'

The team uses PI-RADS (Prostate Imaging – Reporting and Data System) as the reporting and communication tool.

mp-MRI, he explained, is the 'current-state-of-the-art imaging technique' used to assess patients with suspected or confirmed prostate cancer, because it has excellent accuracy in detection or exclusion of high-grade prostate cancer.

Pathologist Professor Sofie Verbeke from the hospital's Department of Pathology offered an insight into tissue processing and sampling after receiving the core prostate biopsies. She outlined the importance of receiving several core biopsies and of every location in separate location-annotated containers in case the needle missed the area of cancer, or detected insignificant cancer but missed the more aggressive cancer area.

Acinar adenocarcinoma is the most common subtype of prostate cancer and graded based on the Gleason score but, she emphasised, making a grading call is not always straightforward.

Urologist Professor Nicolaas Lumen detailed the range of surgical approaches and the decision-making process within that. He can use a finger to assess the T stage but believes MRI is better to differentiate between T2 and T3 tumours.

With a radical prostatectomy there is the choice of open, laparoscopic or robotic surgery: laparoscopic is minimally-invasive but does not have 3-D vision and the instruments are rigid, whereas robotic surgery has 3-D vision and full movement instruments. 'Operating time is decreased with robotic surgery, blood loss is significantly less and there's a shorter stay for the patient in hospital,' he explained. 'Post-operative complications are reduced and pain is reduced with robotic surgery and we have reduced the complication rate to about 1% compared with 5% from open surgery.'

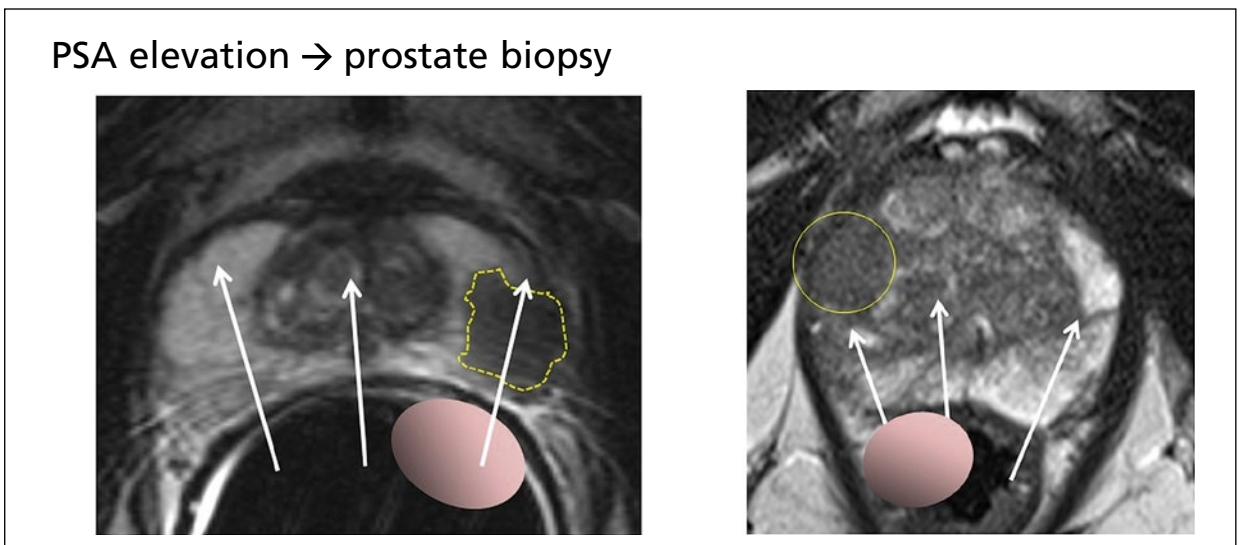
In terms of occurrence of impotence and urinary incontinence, there is no real difference between open and robotic surgery, he said.

MRI is also used to aid patient selection for radical prostatectomy and assess the stages of radical prostatectomy modifications – anterior versus posterior dissection, bladder neck sparing, nerve sparing and urethra sparing – as well as improving functional outcome without jeopardising cancer outcome.

Dose, target delineation and patient positioning remain crucial aspects in delivering radiotherapy treatment to prostate patients.

Radiation oncologist Professor Valerie Fonteyne stressed the importance of having MRI within the treatment planning process to aid with positioning, adding that external beam radiotherapy is an excellent treatment option for patients with prostate cancer and there is now a tendency to move towards shorter radiotherapy regimens.

'Close collaboration with the department of radiology is mandatory in order to improve the outcomes for our prostate cancer patients,' Fonteyne added. (MN)



Prostate cancer in the peripheral zone, palpable with digital rectal examination and hit by the biopsy needle

Prostate cancer anteriorly in a large prostate, not palpable with digital examination and missed by the biopsy needles

The Ghent prostate team (from left) Dr Pieter De Visschere, Prof. Sofie Verbeke, Prof Geert Villeirs, Prof. Valerie Fonteyne and Prof. Nicolaas Lumen.

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Launched: A double-head contrast injector

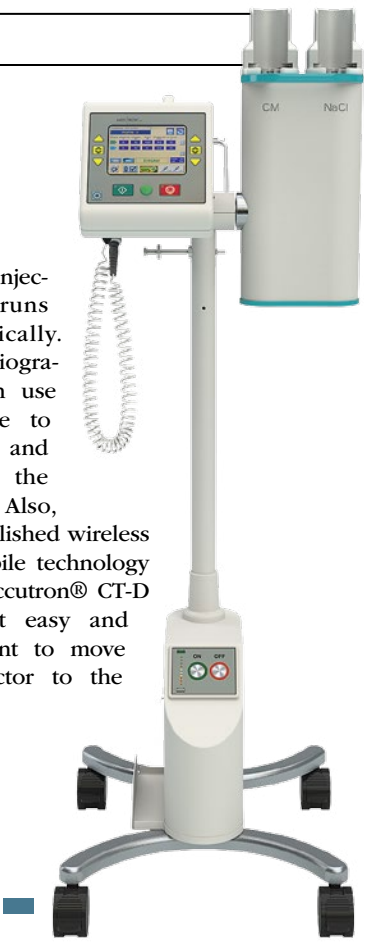
CEM is a clinical application in mammography that combines expertise gained from computed tomography, magnetic resonance imaging and radiography. This functional dual-energy imaging technique gives better tissue differen- tiation with increased visibility of vascular structures and to visualise contrast medium uptake in tissue.

When compared to MRI, CEM tends to provide for fast availability, lower costs, shorter examination times, improved workflow and better imaging of calcifications imaging. Furthermore, it is optimal for patients who are ineligible for an MRI due to i.e. implants, pacemaker, claustrophobia or an inability to assume a prone position (as required in MRI).

The Accutron CT-D, newly released by Medtron AG and reported to be the first and only double head injector for Contrast-Enhanced Mammography (CEM), is working with OEM Mammography equipment providers for CEM or contrast enhanced mammography treatments.

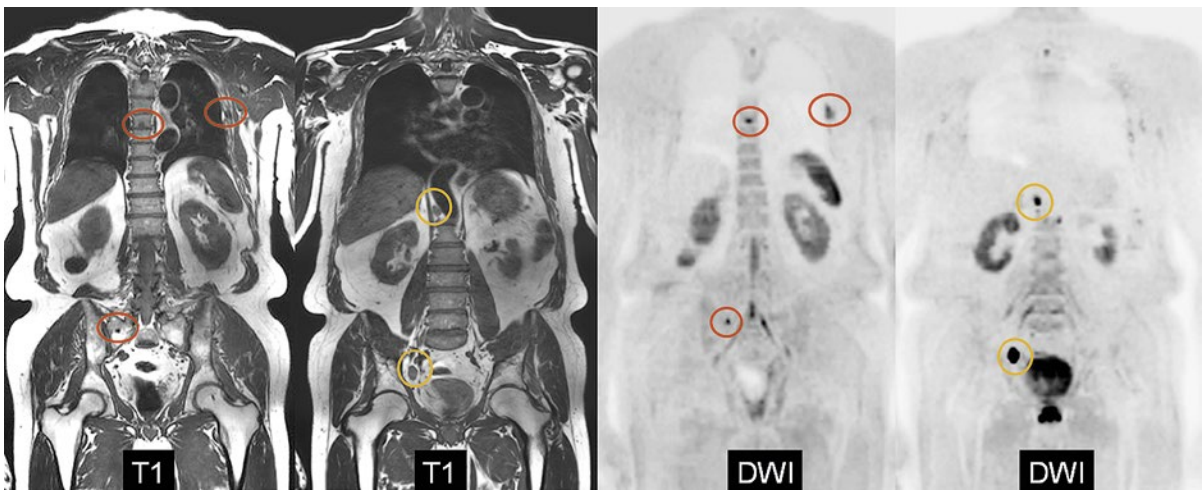
Using the injector alongside CEM imaging procedures ensures a continuous and accurate flow of contrast is provided, the manufacturer explains. It also ensures consistent contrast enhancement of tumour tissue. The system improves diagnostic reporting by accurately delivering a contrast bolus and the possibility of flushing with saline ensures this is compact. Flushing also protects the patient's venous system by reducing the amount of time it is exposed to contrast media, where it could irritate the venous wall. This improves patient safety, Medtron underlines.

'The injector aids the radio- grapher with an intuitive workflow, as the injection runs automatically. The radiographer can use this time to respond and observe the patient. Also, the established wireless and mobile technology of the Accutron® CT-D makes it easy and convenient to move the injector to the patient.'



Prostate cancer heterogeneity negates one perfect method

WB-MRI improves disease evaluation



In one step, whole body MRI including anatomic T1 (left) and functional diffusion weighted imaging (DWI) sequences (right) shows bone (red circles) and lymph node metastases (yellow circles), providing a one-step staging of prostate cancer, non-irradiating and with no need of contrast material or radiotracer

Frederic Lecouvet, from the Catholic University of Louvain in Brussels, Belgium

Dr Irene Burger at the Nuclear Medicine Dept, University Hospital Zürich

Whole-body magnetic resonance imaging (WB-MRI) is championed as offering significant benefits, such as improving disease evaluation for prostate cancer patients.

Report: Mark Nicholls

During an intense session in genito-urinary cancer at the ECR 2019, three key speakers focused on the advantages over conventional imag ing modalities – including bone and CT scans – as well as discussing new PET (Positron Emission Tomography) tracers, and raising concerns about the relevance of the current Prostate Cancer Working Group (PCWG) guidelines within the evolving diagnosis and treatment landscape.

The 'Whole body imaging in metastatic urinary tract and prostate cancer' session was chaired by Professor Anwar Padhani, consultant clinical radiologist at Mount Vernon Cancer Centre in London, who initially posed questions about which techniques to use and when.

He suggested that conventional imaging can lead to poor confidence for assigning clinical states and assessing therapy benefits for bone disease.

Limited imaging tools cannot accurately predict metastatic disease presence and extent, or are unable to identify who is not benefiting early after starting treatment; they also are limited in depicting heterogeneity of biologic behaviour of bone disease, Padhani pointed out.

Professor Frederic Lecouvet, from the Catholic University of Louvain in Brussels, Belgium, explained that metastases from prostate cancer mainly involve the skeleton and lymph nodes, and that two 'modern imaging modalities', WB-MRI and PET, are the current best options, with significant advantages from WB-MRI.

'Whole body MRI – covering the body 'from eyes-to-thighs' – can detect metastatic infiltration of the bone marrow; it also plays a role in detecting lymph node infiltration and, most importantly, it can assess response to treatment,' Lecouvet told delegates.

He compared WB-MRI with PSMA PET-CT in several examples. WB-MRI examinations should include both T1 and STIR 'anatomical' sequences, and 'functional' diffusion sequences, providing a PET-like image. 'The combination details the anatomy and characterises the lesions, yet offers functional information on tissue viability and response to treatment. 'It's an intrinsically hybrid technique,' Lecouvet pointed out.

He demonstrated that WB-MRI provides an all organ approach and looks beyond the skeleton to the nodes, liver and lung. From there, its indications are extending beyond prostate cancer to renal, testicular, ovarian, breast, lung cancers, and to haematological malignancies.

Lecouvet also outlined the MET-RADS-P reporting template for prostate cancer. The recommendations are designed to promote standardisation in the acquisition, interpretation, and reporting of WB-MRI prostate cancer. Used at different time points during the disease, it allows the evaluation of patients for response to treatment of the bone, node and visceral lesions that are recorded and followed-up using morphological and quantitative information. Dr Nina Tunariu, consultant radiologist at the Royal Marsden Hospital, London, concentrated on 'WB-MRI Response and Assessment' and told the congress session that imaging approaches to prostate cancer had changed significantly over the last decade, primarily driven by patient and clinician expectations.

She said bone scans are still requested by clinicians but are no longer necessarily an essential part of the process because they offered late detection and poor accuracy.

Another issue, she said, is that active disease depends on the image you use. 'Prostate cancer is very heterogenous, so there will not be a perfect single technique,' she pointed out. 'Diffusion MRI as part of WB-MRI will help you see more lesions when other imaging techniques are letting you down, while WB-MRI can show a response to treatment whereas CT and a bone scan will not tell how a patient has responded.

'WB-MRI will inform about response and progression early and detail early disease and relapse - it is indeed a very comprehensive technique.'

Early identification of treatment failure, she added, not only spares futile treatment but also potential toxicity and reduces the cost of ineffective treatments as well as decreases the time to the next line of potentially effective treatment.

In conclusion, Tunariu pointed to the imaging response to prostate cancer on WB-MRI: it offers early detection of response, especially in bone lesions; early detection of local relapse; accurate assessment of visceral metastases and of any complications.

Dr Irene Burger from the Department of Nuclear Medicine at University Hospital Zürich, looked at PET and PET/MRI in prostate cancer, and the role of PSMA in prostate cancer.

She pointed out that PSMA is 'not a prostate specific tracer', but also over-expressed in neovasculature and therefore positive on various solid tumours, before briefly comparing its performance with Choline and GRPR (gastrin releasing peptide receptor) PET, noting the latter had the advantage of being more specific within the prostate.

She said choline PET/CT was not useful for the primary tumour but has a higher sensitivity and specificity for lymph node metastasis or distant metastasis than CT, MR or bone scan. It is useful, she added, to detect disease in biochemical recurrence, but only after a PSA of 2 ng/ml, and pointed out that salvage radiotherapy should be performed before PSA of 1.5 ng/ml.

Therefore, whenever available, the PSMA-PET is now used for biochemical recurrence, given the significantly superior detection rate for PSA values as low as 0.2-0.5 ng/ml.

This led to a significant change in the radio oncologic approach for those patients, Burger explained, since early biochemical recurrence does not receive a 'blind' salvage radiotherapy to the prostate bed anymore, but can be targeted to the PSMA-positive lesion, often not localised in the prostate bed.

Burger added that, for staging high risk prostate cancer, PSMA-PET has a superior sensitivity compared to MRI or Choline PET for lymph nodes and distant metastasis.

Collaboration is the driver th

Collaboration of the future: and AI makes three

In view of the advent of personalised medicine and holistic therapy many experts predict the end of healthcare as we know it. However, in many places it is 'healthcare business as usual'. For European Hospital, Dr Christoph Zindel, President Diagnostic Imaging at Siemens Healthineers, explains where he sees radiology bridging the gap between symptom-centred treatment today and the systemic medicine of tomorrow.

Working with Siemens for over 20 years, **Dr Christoph Zindel** was appointed President of Diagnostic Imaging at Siemens Healthineers in 2018. As resident in internal medicine, surgery and nuclear medicine he gained invaluable practical experience that helps him in his task of expanding the boundaries of medical imaging with the help of new technologies.

Interview: Daniela Zimmermann

Current therapy approaches are not as local as often made out to be: 'Indeed there are more systemic illnesses than we think. A weak heart, for example, affects the vascular status and even a malignant tumour cannot be considered a local event. Nevertheless, there are many strong arguments in favour of increasing specialisation, which we also see in radiology. One example: Skeletal scintigraphy in nuclear medicine, a field I have been studying intensively. It evaluates the body as a whole and is thus able to track metastases of breast and prostate cancer via the standard uptake value – SUV.'

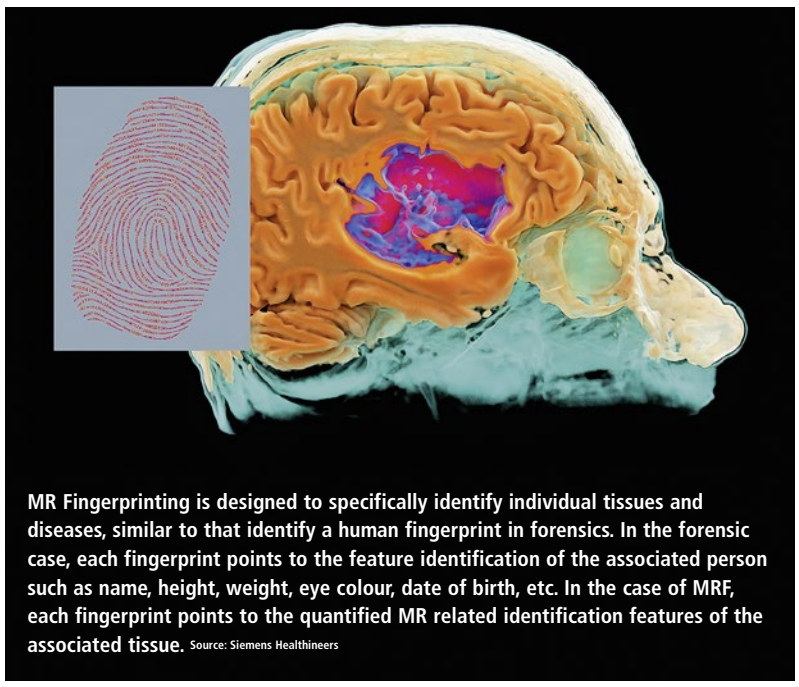
Old procedures, new ideas

Today, even organ-based modalities such as MRI can be used in a way to offer insights into the entire body, for example when the effects of rheumatoid diseases or diabetes mellitus need to be assessed. 'Some procedures have been completely rethought,' Zindel says, and points out that PET/MR, the combination of positron emission tomography and MRI, plays an important role in visualising tumour metabolism.

Whether the holistic perspective or the still widespread practice of treating the symptoms is the road to success depends to a large extent on the type of disease. Zindel is optimistic that new methods, such as gene sequencing and molecular analysis, will offer innovative approaches: 'Precision medicine will come because we will have ever better tools that can show ever more details and interdependencies.'

Achieving the big picture

To keep track of all the different aspects of personalised diagnostics and treatments, the interaction of different tools is increasingly important, Zindel points out. Case in point: radiomics. 'Today algorithms can, to a large extent, independently recognise relevant features in image data – the so-called feature extraction. It's a valuable tool in brain volumetry, for example, since the



MR Fingerprinting is designed to specifically identify individual tissues and diseases, similar to that identify a human fingerprint in forensics. In the forensic case, each fingerprint points to the feature identification of the associated person such as name, height, weight, eye colour, date of birth, etc. In the case of MRF, each fingerprint points to the quantified MR related identification features of the associated tissue. Source: Siemens Healthineers

Imaging options in an abdominal en

CT, MRI, CEUS – which?

The pros and cons of CT (computed tomography), MRI (magnetic resonance imaging) and CEUS (contrast enhanced ultrasound) for emergency abdominal use were highlighted by speakers in an ECR 2019 session under the broader heading: 'Abdominal Emergencies: advanced imaging in daily routine'.

Professor Etienne Danse, from the Imaging Department at St Luc University Hospital, in Louvain's Catholic University, Belgium, focused on CT. In June 2016, his department switched from conventional CT to dual energy CT – which is based on body images at two levels of energy.

While not changing slice thickness, and maintaining image quality, he said in the example of acute pancreatitis, radiation dose was reduced by 30%, because of the ability to convert 'true non-contrast series' with 'virtual non-contrast reconstructed images.'

In the case of acute bleeding, he said, virtual non-contrast can replace true non-contrast.

'Radiation is similar or lower with dual energy CT, and we don't need high contrast iodine concentration,' he explained. 'In some cases, we've reduced dose by 40-60%, and even up to 70%. This is possible when images are reconstructed at a lower energy level and, in this way, the presence of the iodine component in the body is enhanced.'

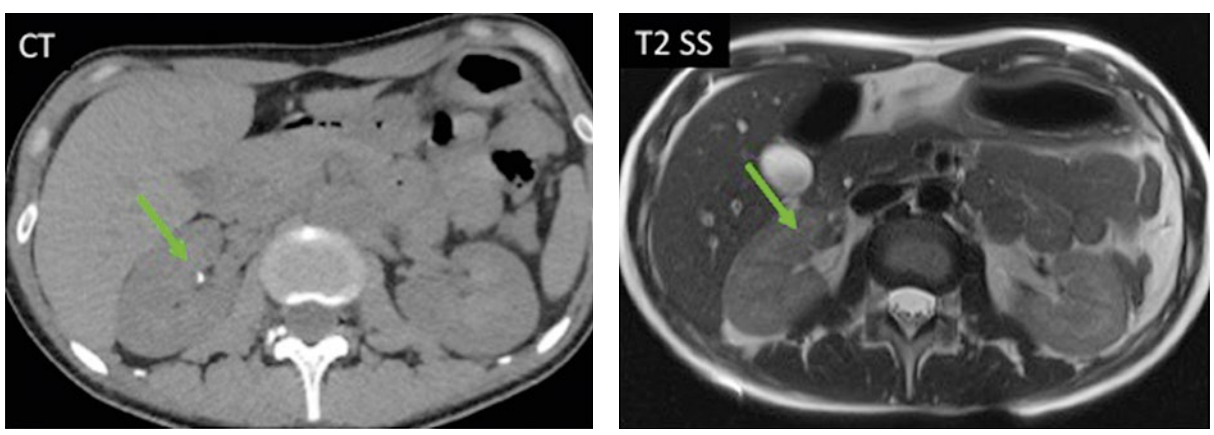
'The dual energy system can be used with a lot of diagnosis for abdomen in adult patients with urinary tract problems, such as stones, hematuria, infection and ischemia; bowel inflammation and cancer, liver inflammation, gall bladder and biliary tract, pancreas and vessels.

Professor Ingrid Millet, from the University of Montpellier, France, spoke about the MRI superiority in acute abdominal pain and in diagnosing specific pathologies, such as acute biliary disease, pancreatitis and gynaecological emergencies. She suggested that, in some circumstances, MRI can be an alternative to CT because of radiation concerns in pregnant women, and paediatric or young adult patients. "Whereas MRI offers an excellent soft tissue contrast, so can be used without IV contrast and has no ionising radiation, it has low accessibility, is expensive and time consuming, is sensitive to motion artefact in long examinations and has not been assessed yet for unselected abdominal pathologies.'

CT, she said, is fast, widely available and has a high diagnostic performance for many acute abdominal diseases, but uses ionising radiation and iodine contrast and is less accurate in characterising mass content.

However, Millet conceded: 'MRI is less precise than CT in diagnosing bowel perforation. With paediatric patients, ultrasound remains the first imaging modality to investigate acute abdominal pain while MRI can be used as a second line, especially for obese children or those older than nine, and for acute pelvic pain in paediatric female patients.' Where MRI offers significant benefits is in characterisation of fluids and masses and sensitivity in pinpointing inflammation.

Parallel imaging allows for fast acquisition, yet concerns remain with MRI over its ability to diagnose when



Non obstructive right kidney stone that would not appear on usual MRI single shot T2 weighted images. In an abdominal emergency, radiologists have a number of imaging options. The one they choose will depend on factors such as a patient's symptoms, age, condition, plus which modality presents less risk and offers the best diagnostic option.

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hat enhances patient welfare

ventricle surfaces no longer need to be added up manually. The computers do the drudgery. At the same time the different brain regions are labelled automatically, which is very helpful in the diagnosis of neurodegenerative diseases.'

When these and other results, let's say of liquid biopsy, are linked – or, to be precise, if a computer is asked to link them – a full picture of the patient is generated. This is an immense added value for therapy but also for prevention purposes.

No doubt there are obstacles to overcome, for example non-standardised procedures, such as MRI, where every radiologist uses the sequences and protocols he or she considers most appropriate in any given case. Since there are no reference values, such as Hounsfield units in CT, data integration poses a challenge. 'Consensus is virtually impossible to reach, since an image that is considered good by a radiologist in the USA, might be viewed sceptically in Asia and Europe,' Zindel says, but he adds a way out 'might be MR fingerprinting, which, for the first time, offers quantifiable data.'

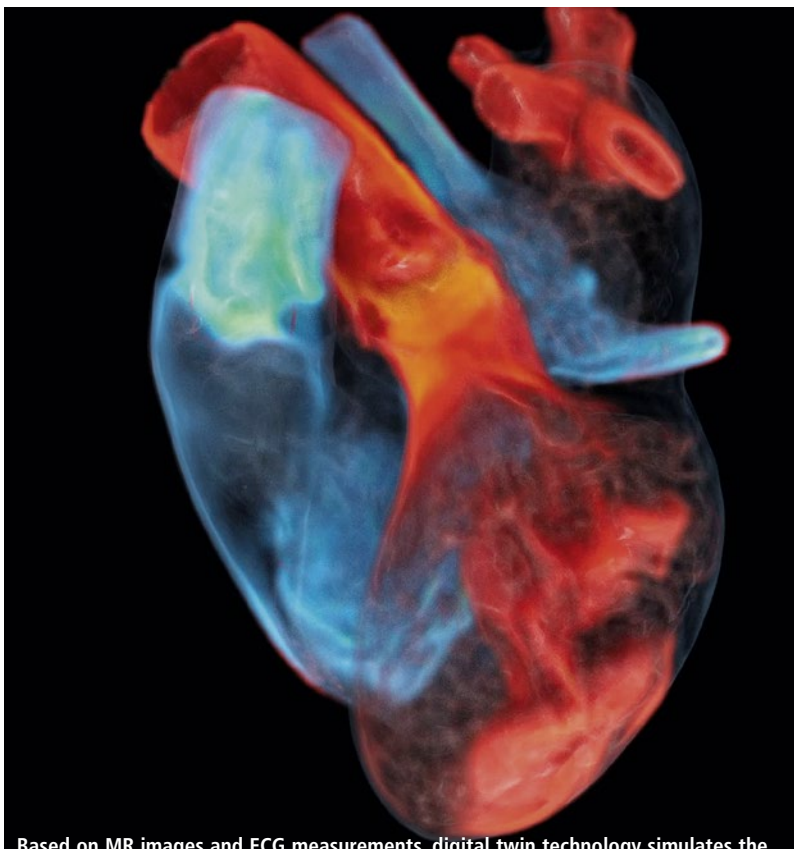
A new and crucial role

While Zindel, unlike many others in the industry, does not consider artificial intelligence (AI) to be a panacea, he is convinced that it will drive progress in several areas of healthcare: 'Smartly used, AI has enormous potential, above all when it comes to simplifying and accelerating processes – which in turn will improve productivity.' While the machine takes on the role of supporter, humans will continue to make the final decisions – a scenario which will not change any time soon, says Zindel. The algorithm for image data analysis can already discard irrelevant images; thus the radiologist has to deal with a much smaller number of images than before. Drudge work, such as the manual counting of lesions, is history since AI performs this task faster and better.

In differential diagnostics, in particular, Zindel expects AT, combined with Big Data and radiogenomics, will trigger quality leaps: 'Going forward we may well have a troika of physician, patient and AI that jointly stratifies the patient. Not only the cooperation between radiology and pathology will profit from increased standardisation, the patients will also benefit because AI-processed data will provide information the patient can understand.'

In this scenario, Zindel says, the radiologist will assume a new, but still crucial role as a guide navigating the sea of patient data. 'The important issue about Big Data is not the fact that we need more data, but that we must be able to cull the relevant information from the sheer mass of data.'

In the long run, this development will render proprietary data silos obsolete, since going it alone is not an option with huge data volumes. 'The future belongs to collaboration; it is the driver that enhances patient welfare.' Thus, collaboration will be the starting point of future-proof business models – models that are no longer based on services rendered but on value generated.



Based on MR images and ECG measurements, digital twin technology simulates the physiological processes of a patient's organ. Virtual planning is used to visualise responses to treatment before the intervention. Siemens Healthineers is developing algorithms that generate digital models of organs based on vast amounts of data.
Source: Siemens Healthineers

PET and MRI provide complementary information on several clinical applications, including cancer. While MRI offers high-resolution imaging of anatomical structures with high soft-tissue contrast, PET visualises metabolic processes inside the body. The combination of these modalities has great potential for improved detection and therapy monitoring in oncology.
Source: mMR Munich (TUM/LMU)

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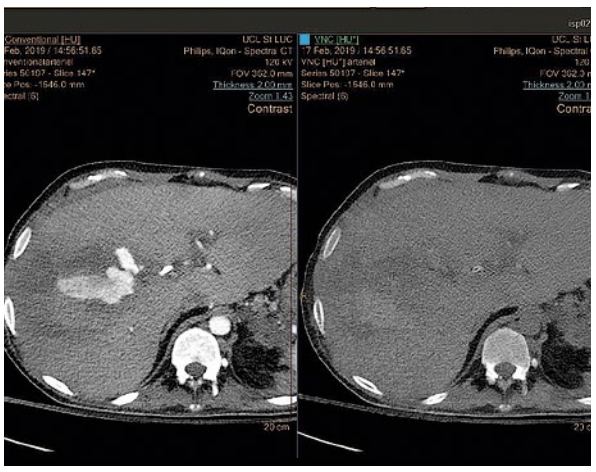


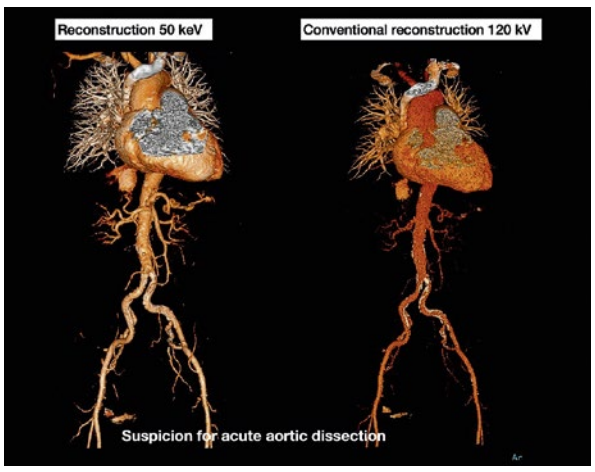


Illustration of acute, ongoing arterial bleeding in the liver with added value of virtual non-contrast series: On the left picture from the arterial series a huge hyper-attenuating zone (arrow) is visible above a moderately hyperattenuating mass (asterisk). On the right, on the virtual non-contrast reconstructed series, the acute bleeding zone is removed, due to the presence of a high percentage of iodine (active extravasation). The moderate hyper-attenuated mass did not change because of the absence of iodine

Illustration of added value of lower keV reconstructed images when the vascular phase is of poor quality, like in this case of suspicion for an acute aortic dissection

there is diffuse abdominal pain, its low sensitivity for free intraperitoneal gas and for non-obstructive renal stones, as well as a lower spatial resolution than CT.

Millet explained ways to optimise MRI protocols, such as by limiting the number of sequences and multiplanar acquisitions as well as using compressed sensing technologies that allow a decrease in acquisition time and would permit T1 weighted images acquisition in free breathing with very low temporal resolution.

In future, she hopes MRI will replace CT as a first line imaging modality for appendicitis/diverticulitis and also to investigate bowel obstruction and diagnose bowel perforation, and accurately assess urologic emergencies.

However, for now, 'There is a need for standardisation of MRI protocols, assessment of enhanced sequences added-value, and for further radiologist training and education to be at ease with MRI images and their interpretation,' she pointed out. One area that has proved effective to diagnose abdominal conditions in an emergency setting is contrast enhanced ultrasound. 'Adding contrast increases the efficiencies of ultrasound in the emergency setting, and CEUS is also very useful in follow-up,' said Dr Teresa Fontanilla, from the Hospital Universitario Puerta de Hierro-Majadahonda in Madrid, Spain.

Fontanilla has looked at the CEUS role in abdominal inflammatory and infectious conditions, highlighting the use of contrast when viewing hepatic abscess. 'CEUS can help when there is an indeterminate suspicious mass and to determine the degree of liquefication to decide on drainage and antibiotics, or just antibiotic treatment.'

In addition, she suggested CEUS is a valid tool for gastrointestinal tract and gynaecologic inflammatory lesions and at times for cholecystitis and prostatitis, offering delegates visible examples.

CEUS can identify inflammatory bowel disease complications, appendicitis and diverticulitis complications and differentiate abscesses from phlegmon and measure abscess size, she added.

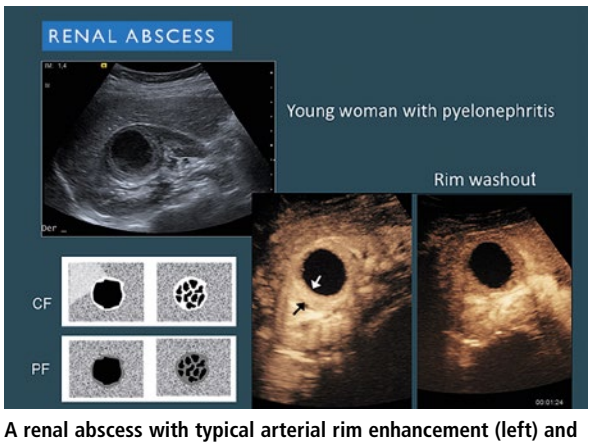
There are limitations to CEUS, e.g. a poor window and difficulty in detection of very small lesions, but, she said, 'CEUS is an efficient, case-solving tool in selected cases in the emergency setting and has a general-purpose role in any abdominal inflammatory condition. It can also be used if there is a suspicion of drainage catheter obstruction or fistula and for follow-up away from the emergency setting. 'It offers real-time, quick, assessment without radiation and nephrotoxicity.' However, she added, the big advantage with CEUS is in direct patient contact,often at the bedside.

(MN)

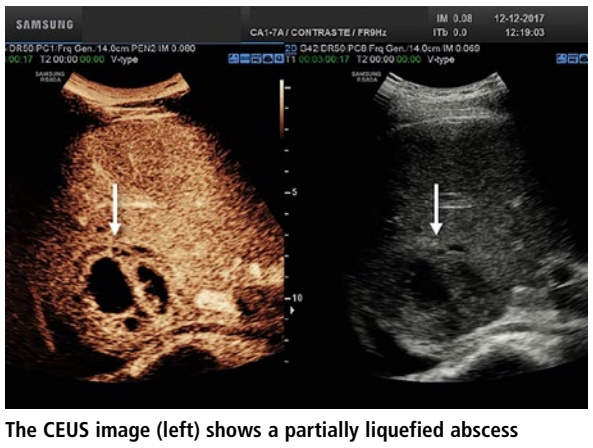
Professor Etienne Danse, from St Luc University Hospital, at Louvain's Catholic University, Belgium

Professor Ingrid Millet works in the University of Montpellier, France

Teresa Fontanilla is from Hospital Universitario Puerta de Hierro-Majadahonda in Madrid, Spain



A renal abscess with typical arterial rim enhancement (left) and washout (right) is nicely depicted in the CEUS images of this young woman in high fever



The CEUS image (left) shows a partially liquefied abscess (arrow), which is less conspicuous in the basal ultrasound image (right)

Innovation: updating an established ultrasound scanner

Stripped and new new new

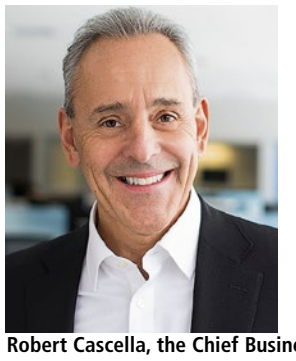
Bringing data together that belongs together – for Robert Cascella this aim embodies the future of diagnostics. 'We are creating a seamless network of people, technologies and data to achieve the best possible result for the patient,' Cascella, the Chief Business Leader Precision Diagnosis at Philips, explained. 'Isolated information is often not sufficient to meet the high expectations of radiologists in a world of value-oriented healthcare. 'This was demonstrated with the introduction of the new Illumeo software for workflow optimisation and the CT system Incisive, which integrates innovations from the fields of lifecycle management, workflow and imaging.

Philips has ramped up is ultrasound platform, Epiq, considerably. Although the most recent device in this range, the Epic Elite, does not look very different to its predecessors, almost everything is new inside, according to Professor Dirk-André Clevert, head of the interdisciplinary ultrasound centre at Munich University Hospital, who introduced the system at ECR 2019. 'The device was basically completely stripped down – new hardware, new software, a new engine and new transducer.'

A smart probe

The latter contains some exciting innovations: The transducers with xMatrix-XL 14-3- linear array facilitate high resolution visualisation of volumes over time, i.e. 4-D imaging. 65,000 elements – conventional probes have up to 256 – and sophisticated assistance systems make it possible to achieve user-independent, clear spatial images. 'Previously, it had been impossible to work with such a large number of elements due to the huge volume of data. However, with the new design, most of the processing has been moved into the transducer, which increases the resolution considerably, Clevert explained. This tweak has made it possible to circumvent the previous bottleneck involved in transducer design as the data does not need to travel along the entire cable.

The EPIQ Elite Ultrasound Solution for Vascular Assessment allows clinicians to make confident assessment and diagnosis of vascular conditions. Source: Philips



Robert Cascella, the Chief Business Leader Precision Diagnosis at Philips

Specific features of this device include the MicroFlow Imaging modus to visualise anatomic structures with slow and weak blood flow in the tissue – making the scanner the first Philips ultrasound solution for vascular evaluation and diagnosis. The technology core is sophisticated artefact reduction, which helps to visualise blood flow in structures with small vessels without any impairments from artefacts.

The new modus is primarily to be used to detect strokes, still the second most common cause of death worldwide, with 270,000 cases a year and one of the leading causes of disabilities in adulthood. As around 10-20% of all strokes are associated with atherosclerotic lesions of the extracranial carotid artery, MicroFlow technology combined with the efficient linear probe can deliver important additional information.

The innovative 3-D/4-D imaging also offers new opportunities for investigations into numerous other vascular problems. The walls of the vessels can be clearly defined, and plaque morphology, which is predictive for cerebral ischaemia, as well as intraluminal clots, can be captured reliably.

The additional iSlice function provides information on the configuration and composition of the plaques.

Last but not least, there is also a large number of special functions for Obstetrics and Gynaecology, such as improvement of image quality and lifelike 3-D scans to examine of foetuses.

(DZ)

In 2003 **Professor Dirk-André Clevert** moved from his native Berlin to Munich to lead the Interdisciplinary Ultrasound Centre at University Hospital Munich, having begun his medical career at the MRI Diagnostics Institute Westend in Berlin and the internal medicine department at the Waldkrankenhaus Gransee. Following those, he spent three years as a specialist registrar in Passau's radiology department. As course director and congress president, Clevert organises national and international ultrasound courses and congresses. He was awarded an honorary doctorate during the 80th anniversary of the Medical Faculty of Tbilisi State Medical University.

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Founded by Heinz-Jürgen Witzke
ISSN 0942-9085

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

Subscription rate
6 issues: 42 Euro, Single copy: 7 Euro.
Send order and cheque to:
European Hospital Subscription Dept

Printed by: WVD, Möhrfelden, Germany

Publication frequency: bi-monthly

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WHO: 'Refugees do not bring diseases to western shores'

Detecting migrant health risks

The migrant population is fast growing and heterogeneous. Experts at a session held during the European Congress of Radiology (ECR 2019) concluded that radiologists can play a key role in detecting and differentiating related diseases.

Migration is a growing phenomenon and has an impact on health, according to Jozef Bartovic from the World Health Organisation (WHO) in Copenhagen, Denmark. 'We've seen a huge increase in migration over the last few decades, and about 10% of global population today are international migrants. There is a huge heterogeneity of resources, backgrounds, exposure to risks, which are all important to consider in healthcare. Refugees are just 7% of all migrants,' he said.

Key migration factors can lead to health problems before, during and after migration. War impacts on mental health before and after migration. Violence during migration, for instance smuggling, burns or drowning, has consequences on a migrant's health. Discrimination and low levels of integration in the host country can also trigger health problems.

The WHO refugees and migrants' health in Europe report states: Migrants do not bring diseases with them to their country of destination. 'Refugees and migrants are generally in good health, but can be at risk of falling ill during the transit period and in the receiving countries, due to poor living conditions and adjustment to their new lifestyle,' Bartovic pointed out.

Considering the incubation period of most bacterial and viral infections, most migrants will be either cured or dead by the time they arrive in the destination country. Living in a refugee camp, for instance, can provoke a number of diseases that can be fatal and take up considerable healthcare funds if untreated. Very early detection and correct treatment of diseases is key.

'The links between migration and radiology are worth exploring, especially regarding access to services, legal barriers, health service capacity and continuity of care,' he said.

TB or not TB

The most common migration diseases relevant to radiology are pulmonary and extrapulmonary tuberculosis (TB), according to Tim Weber, senior physician at the Institute of Diagnostic and Interventional Radiology in Heidelberg. 'TB is the most common infectious disease in the migrant population. There's a difference between TB in the migrant population, which affects mainly young people, and TB in the host population, where it's typically a disease of the elderly.'

The main challenge for radiologists in pulmonary TB is to differentiate between active and inactive TB.

Continued on page 24

Tim Weber MD is a senior physician at the Institute of Diagnostic and Interventional Radiology, in Heidelberg University Hospital, Germany.

Technical officer **Jozef Bartovic** at WHO/Euro, contributes to the PHAME project, the Knowledge Hub and the Migration and Health Knowledge Management Project. Previously, working for the Regional Commission for Western Asia of the UN Secretariat in Beirut, Lebanon, he covered migration and displacement issues in the Arab region.

Originally from Slovakia, after completing political studies he worked in the UK for the Ministry of Health, Public Health England (Health Protection Agency) and the NHS on screening programs, sexual and reproductive health and primary care access.

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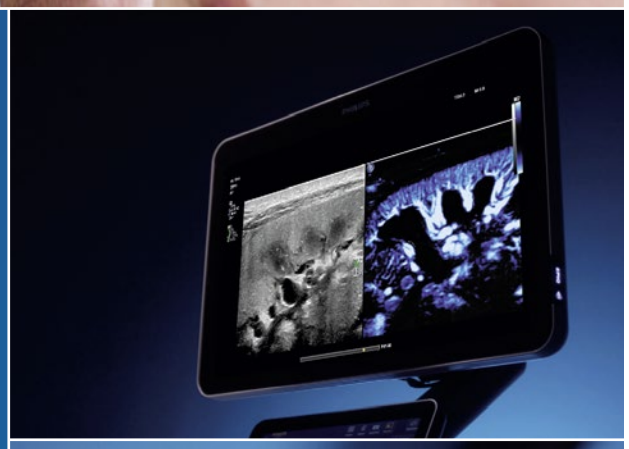


Antibodies PD-1 and PD-L1 are a quantum leap in cancer therapy

Boosting our immune surveillance

Immuno-oncology is a therapy in which the body's immune system treats a tumour. Dr Eric Borges, from the Research and Development Centre at Boehringer Ingelheim Pharma GmbH in Germany, explains why this is revolutionary.

© Boehringer Ingelheim

Eric Borges: 'We really are moving towards a new era of cancer treatment, which is incredibly exciting and extremely motivating for me.'

Unlike conventional cancer therapies, with immuno-oncology the tumour cell is not the direct target, it's the patient's immune system. The medication stimulates this to then fight the cancer cells.

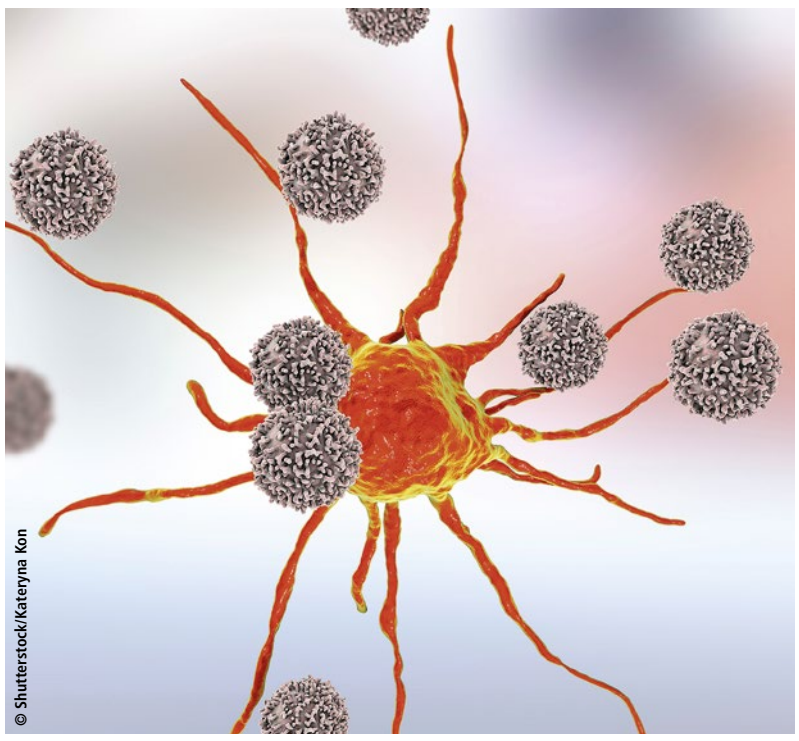
The immune system is trained to detect foreign structures in the body and to remove them. Bacteria, viruses, toxins – it detects anything foreign and destroys it. With immuno-oncology we try to impact on the immune system so that it recognises tumour cells as being foreign and destroys them.

With conventional cancer treatments we have used our cancer cells findings to develop new drugs. As cancer cells divide faster than most normal cells, we developed chemotherapeutic agents that destroy the fast-growing cells. The discovery of tumour-relevant mutations in cancer cells was utilised to develop targeted drugs to neutralise the effect of such mutations. Unfortunately, tumour cells frequently find ways to elude the effects of these drugs and develop resistances. The immune system, however, reacts immediately to changes in the cancer cell. It can adapt to the changed situation and so can better prevent the development of resistances.

Immunotherapy – a breakthrough

Patients who respond to this treatment have real chances of becoming free of symptoms, or possibly even tumours, for many years. Some tumours have been gone for more than ten years, even those with such life-threatening diseases as black melanoma. This has only been observed in a small number of patients treated, but immunotherapy could increase the chances of real cures for cancer significantly.

At the moment it applies mainly to patients whose tumours have high mutation rates, which can be classed as 'immuno-active' or 'hot' types of tumours that benefit from immunotherapy – including melanoma. Its development is strongly favoured by increased UV exposure, i.e. sunbathing without sunscreen, which can lead to a concentration of skin mutations, and later to degeneracy of the mutated cells, i.e. a cancerous growth.



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Melanoma cells usually have many mutations and are therefore easy to detect by the immune system. But, the cancer still manages to elude this immune surveillance. The tumour generates an environment that strongly reduces the activity of the immune cells, so they can no longer attack them – so the melanoma grows. So-called 'checkpoint inhibitors' have been available for a while, primarily monoclonal antibodies against PD-1 and its ligand PD-L1, which neutralise one of the essential immune-suppressing mechanisms of the tumour. This causes the tumour-specific immune cells to become active again and to attack and destroy the tumour cells.

These PD-1 and PD-L1 specific antibodies represent a quantum leap in cancer treatment, and their potential, combined with other therapeutic agents, is being trialled in more than 1,000 clinical studies. These antibodies are currently licensed to treat many cancers, including melanoma, lung, kidney and bladder cancers, and also certain types of lymphoma, bowel or uterine cancer.

Presently, we see the most success with 'hot' tumours. But there are also high expectations for the development of improved chances of cures for cold tumours.

In immuno-oncology we distinguish between 'cold' and 'hot' tumours. We refer to tumours as hot when the appropriate immune cells are already located in the tumour and only the local immune-suppressing effect of the tumour cells prevents the immune reaction. When this blockade is lifted, through PD-1 or PD-L1 antibodies for instance, the immune system can take control and remove tumour cells.

From cold to hot

However, where these PD-1 antibodies and therefore immunotherapy in its current form does not work is in cold tumours. They contain none, or only few, immune cells and therefore the tumour has no inflammatory reaction. The challenge will be to heat up these cold tumours so that currently available immunotherapies will also work. There are many concepts for this in preclinical or early clinical studies; with most this amounts to combination therapy, with one drug primarily changing the cold tumour into a hot one and the second drug neutralising the local immunosuppression.

We are literally going through a very hot phase; researchers are experimenting a lot. Among others, we are testing small molecules, antibodies, cytokines, oncolytic viruses and vaccines, i.e. everything that's suitable for the generation of an efficient immune reaction against the tumour cells. Research is intense in this field – I hope we'll see many more breakthroughs in the near future.

Immunotherapy limitations

These are seen in treatment of cold tumours. One of the coldest types of cancer is pancreatic cancer; many cases are still fatal. Breast cancer and prostate cancer are also colder tumours – but, basically, cold tumours can be seen in almost all indications. Immunotherapy is therefore not so much aimed at the different indications but at the immune and mutation status of individual tumours. In other words: Each tumour indication will only ever have a certain rate of response for immunotherapy. For instance, melanoma is currently around 40%. This means, unfortunately, that the other 60% will not respond. For lung cancer the rate of those responding to existing immunotherapy with PD-1 antibodies is currently only around 15-20%. Combined with chemotherapy though the response rate is considerably higher. Therefore, we are hopeful that further combination therapies will continue to increase the success of immuno-oncology and will facilitate better treatment options for patients.

The differentiation between hot and cold applies to all cancer types. For skin cancer, the proportion of hot tumours is around 40%, for bowel cancer around 10-15%. For pancreatic cancer it's extremely low. We are working to increase this rate with new treatments and I'm convinced a lot will happen in the next five years. The biggest success with cold tumours is likely to be achieved with combination strategies.

As with HIV, might cancer become a chronic disease?

I'm convinced this objective is realistic – with one difference. With current HIV treatment, patients must take medication for a lifetime to prevent disease recurrence. However, after successful treatment, immunotherapy can be stopped without the tumour starting to grow again. In some cases, patients have remained tumour-free for more than ten years after treatment ends. This is because functioning immune surveillance prevents renewed tumour growth.

However, patients free of symptoms for many years after successful immunotherapies is still small in number – melanoma is around 10%; lung cancer significantly lower.

This is the second big difference to anti-viral treatment as used in HIV therapy: With cancerous diseases we are looking at very heterogeneous disease patterns, where individual patients respond in very different ways to the same type of treatment. Our objective will be to develop a wide range of highly effective immunotherapeutic agents while simultaneously gaining a better understanding of which drugs promise the best treatment options for the respective patients.

Source: www.pharma-fakten.de

Detecting migrants health risks

Continued from page 23

Active TB typically presents as consolidations with cavitations and formation of centrilobular nodules due to bronchiolitis after bronchogenic spread of microbacteria. Necrotising adenopathy and pleural effusion are further signs that should alert the radiologist. Inactive TB is characterised by fibronodular scarring, volume loss and calcifications. An important feature in ambiguous cases is stability of imaging findings over time, so follow-up is recommended.

Pulmonary TB is atypical in HIV+ patients; especially in patients with CD4 lympho count <20/nm typical features of TB. 'Typical features of TB like cavitation or adenopathy are lacking, and other unspecific consolidations are primary imaging findings,' Weber said.

Rapid diagnosis in this fragile population is important. also of note: TB risk is 20 times higher in HIV + patients.

Most radiologists know that extrapulmonary TB can affect any organ, because haematogenous spread of microbacteria is almost always present during primary TB. Extrapulmonary TB can be abscess forming, but can also present with soft tissue infiltration.

'This is also a reason why extrapulmonary TB is known as the great imitator, mimicking a variety of infections and neoplastic diseases,' Weber explained.

Sometimes no imaging findings can help distinguish between intestinal TB – TB ileum - and Crohn's disease. One can detect fistula and chronic inflammation, e.g. proliferation of mesentery fat, possibly present in both diseases. In pulmonary TB, the main task is to differentiate between active vs. inactive TB, and consider TB in any pulmonary infiltrate.'Extrapulmonary tuberculosis should be considered in any suggested inflammatory or neoplastic disorder,." he advised

Worm-caused diseases

Cystic echinococcosis (CE) and schistosomiasis are two other common conditions that mainly affect migrants.

CE is caused by dog tapeworm and has a global distribution. Almost eradicated in most western industrial countries, there is only scarce data on prevalence in migrants - however, CE will be diagnosed in a large number of refugees or migrants.

CE causes cystic expansive mass, which can grow in any part of the body, mostly the liver or the lung. Serology test can be negative in a number of patients and imaging is essential for diagnosis.

CE shows with specific pathognomonic signs on imaging, such as the water-lily sign (CE 1), the rosette sign (CE 2), the Swiss cheese sign (CE 3b) and the ball of wood (CE 4).

'The major CE feature is that there is complete absence of vascularity, thus contrast imaging studies should be performed to exclude neoplasm,' Weber said.

Schistosomiasis, a set of diseases caused by trematode worms, or blood flukes, is very common in tropical and subtropical regions; more than 150 million people are affected in sub-Saharan Africa alone.

The worms produce eggs that are embolised via the portal vein to the liver, inducing chronic liver inflammation, which can lead to periportal hepatic fibrosis or Symmer's pipe stem fibrosis.

Here also, imaging can help, notably to differentiate between liver cirrhosis and schistosomiasis.

(MR)