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Physician burnout cases are rising

In a special report for European Hospital, Mark Nicholls looks at the growing issue of physician burnout

Longer hours, more demanding working practices, complex cases and increased administration are taking their toll on physicians as growing numbers, across a range of specialties, report signs of burnout.

All this despite technological advances such as artificial intelligence and machine learning to aid diagnosis, read and interpret images, improve workflow and enhance decision-making.

Recognised as a global healthcare issue across all disciplines – particularly cardiology, radiology, urology, neurology and among A&E and intensive care practitioners – physician burnout is the focus of increasing studies and research.

The Mayo Clinic in Rochester, Massachusetts, aims to recognise the symptoms of physician burnout and offer potential remedies, while a United Kingdom study highlights how physician burnout is affecting healthcare delivery.

'Angry, irritable, impatient'

The Medscape National Physician Burnout and Depression Report 2018 – a US-based survey of 15,000 physicians across 29 specialties – found that more than 40% were reporting evidence of burnout. Low morale, overwork, rising caseloads and increased bureaucracy led to burn-out with growing numbers leaving the profession, suffering



mental and physical health issues, or committing suicide.

The survey showed that, within cardiology for example, 43% of physicians were affected. Those most

affected by burnout were critical care specialists and neurologists (both 48%) and the least affected were plastic surgeons (23%).

Addressing a special 2018 ESC congress session in Munich, Dr Anthony DeMaria from the Division of Cardiovascular Medicine at the University of California, San Diego, noted that the burned-out physician 'is angry, irritable, impatient, has increased absenteeism, decreased productivity and decreased quality of care'.

Significantly, the age group experiencing the greatest incidence of burnout (50%) is 45–54-year-olds. 'One might have expected burnout to be more prevalent in older physicians who have become more frustrated with increased bureaucracy, but this is not the case,' said DeMaria.

In terms of contributing factors, 56% of physicians who reported burnout cited excess bureaucracy. Other causes included long working hours (39%), lack of respect from colleagues (26%), increasing computerisation of practice (24%), insufficient compensation (24%) and lack of control/autonomy (21%).



Dr Maria Panagioti is a Senior Research Fellow at the Centre for Primary Care at the University of Manchester. Her research includes understanding and preventing burnout and psychological distress in healthcare professionals.



Dr Liselotte Dyrbye is a consultant in Division of Community Internal Medicine at Mayo Clinic and Professor of Medical Education and Professor of Medicine. She co-directs the Mayo Clinic Department of Medicine Physician Well-Being Program with a key focus on physician, resident and medical student well-being, studying the prevalence, drivers and consequences of burnout and mitigating strategies.

'Doctors are reporting they spend more and more time dealing with computers and documents, and less time interacting with their patients and practising medicine,' DeMaria continued. To address the problem, he believes it is crucial to look at the causes, notably workload and impact on lifestyle.

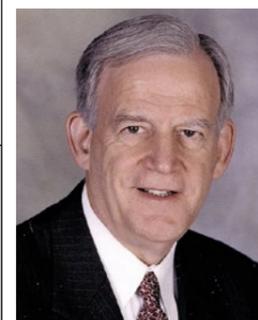
With the survey showing 13 percent of cardiologists also experiencing depression as well as burnout, DeMaria pointed out: 'Cardiology is the "most unhappy" speciality, but also the least likely to seek professional help.'

Destructive coping mechanisms

Another trend is of physicians leaving patient care for non-clinical jobs with drug or insurance companies, a pattern that has major implications for projected physician shortages. 'To cope with burnout,' DeMaria explained, 'some turn to exercise, talk with family and sleep but others turn to food and alcohol, smoking or take prescription drugs. Physicians often turn to potential coping mechanisms that are very destructive.'

Physicians are also the highest group that commits suicide – nearly double that of other professions, with 400 a year in the USA. 'They have the knowledge and the means to do it but are also the least reluctant to come forward to seek help.'

Burnout is also prominent among medical students and residents; a Mayo Clinic study shows that resident physician burnout in the USA is widespread.



Dr Anthony DeMaria from the UC San Diego School of Medicine, Division of Cardiovascular Medicine, is the Judith and Jack White Chair in Cardiology and founding director of the Sulpizio Cardiovascular Center at UCSD. With research interests in cardiac imaging, he regularly participates in trials involving non-invasive methods to diagnose and treat heart disease.

Defining burnout as a dangerous mix of exhaustion and depersonalisation that contributes to physicians making mistakes within healthcare, the study to explore burnout predictors (pub: Journal of the American Medical Association) longitudinally followed 3,600 medical trainees from medical school into residency. 45% of respondents experienced at least one major burnout symptom, with those in urology, neurology, emergency medicine and general surgery at the highest risk.

'Our data,' said lead researcher Dr Liselotte Dyrbye, 'show wide variability in the prevalence of burnout by clinical specialty, and that anxiety, social support and empathy during medical school relate to the risk of burnout during residency.'

Specific concerns about burnout amongst radiologists have been raised by Dr Richard Cohan and Dr Matthew Davenport from the Department of Radiology at the University of Michigan Hospital in Ann Arbor.

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Dr Malcolm Bell is an interventional cardiologist with special interests in complex percutaneous coronary intervention, transradial approach, and adjunctive antiplatelet and anticoagulant therapy. An attending consultant in the Cardiac Intensive Care Unit, he is Vice Chair of the Department of Cardiovascular Medicine at Mayo Clinic.



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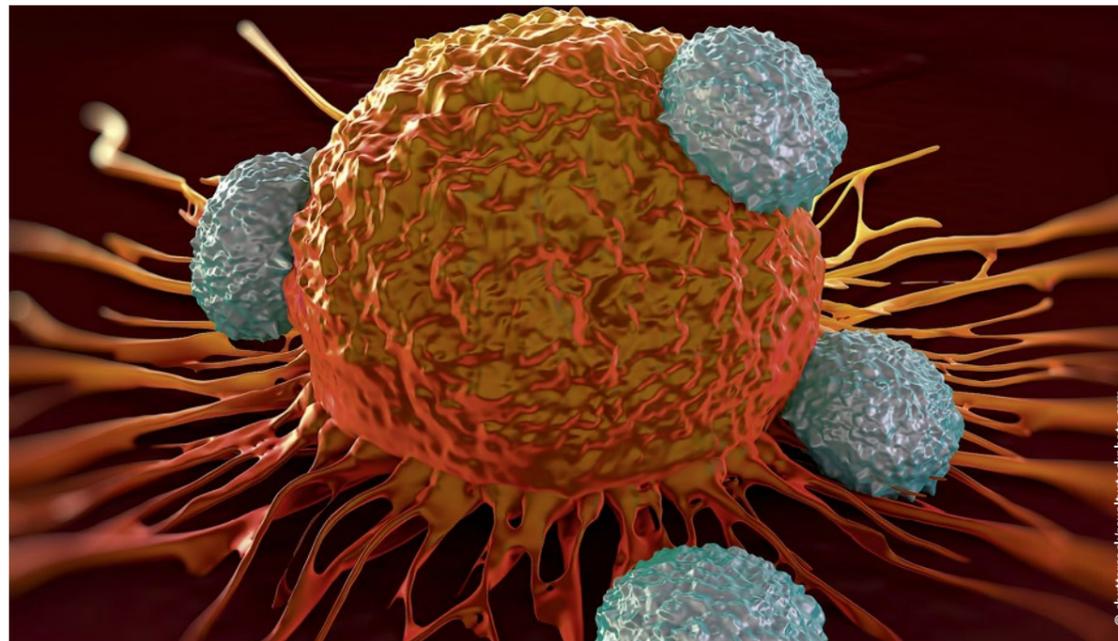
Cancer: the innovation wave

Report: Michael Krassnitzer

In haematology and medical oncology there is always something new. However, the increasing stratification of cancer therapies presents an enormous challenge for clinical research.

Tumour cells – those altered genetically by mutation and thus ought to be recognised by the immune system and destroyed – manage to apply diverse molecular tricks to avoid attack by the immune system. Thus, they are invisible to the T-cells that wander through the organism hunting for foreign and modified substances. At the end of August, an innovative therapy CAR-T was approved for use in Europe. This treatment aims to ensure that T-cells identify tumours and can recognise them as a threat to the body.

To this end, white blood cells are extracted from the patient and T-cells are derived from these in the laboratory. An inactive virus is inserted into them. The DNA in the T-cells adopts the virus' heritage, expanded with a special gene. This



gene ensures that the T-cells carry a certain protein in their shell, the chimeric antigen receptor against CD19. The receptor can recognise cancer cells in a patient and bond with them accurately. Chemotherapy

T-cells attacking cancer cell illustration of microscopic photos

is then used to kill as many of the patient's T-cells as possible and the genetically modified CAR-T-cells

are introduced by an infusion into the patient's bloodstream. These cells multiply in the body and now actively fight tumour cells.

T-cell engineering was one of the focal points of this year's meeting

of the Austrian, German and Swiss specialist societies for haematology and medical oncology (DGHO, OeGHO, SGMO und SGH+SSH), held in Vienna this September.

The CAR-T therapy is an expansion of the therapeutic portfolio by addition of a new principle for treatment of patients with malignant haematological illnesses, where initial studies show it to be in part highly effective. 'In clinical studies, we reach response rates from 60 to 90% with acute leukaemia and 30 - 50% for non-Hodgkin lymphomas in advanced stages of illness. That is far more than with other therapies for these patients, who are very difficult to treat,' explained Dr Hildegard Greinix, who heads the clinical department at the LKH – University Hospital Graz, and also serves as congress president of the annual meeting.

CAR-T-cells are just one example of the enormous therapeutic progress that has been reported, particularly in immunology-based anti-tumour therapies in recent years. The innovation wave rolls on with targeted cancer therapies oriented

Among advances, immuno-oncology has good recovery prospects

Revolution and evolution in oncology

Report: Eva Britsch

Dr Georg Ralle, General Secretary of the association 'Network against Colon Cancer' since 2012 as well as moderator of the symposium 'The New Measurement of Oncology', hosted by the National Centre for Tumour Diseases Heidelberg (NCT), clearly voices his dissatisfaction

with the German 'wait it out mentality'. He sharply criticised the Federal Joint Committee (G-BA) and here also explicitly the committee's chairman Josef Hecken.

Colorectal cancer prevention needs a boost

Ralle garnishes his criticism with a portion of cynicism: 'Actually, one

should think that the respective Federal Minister of Health is exerting pressure on Hecken to keep to agreements; but, when Hecken sees the number on the phone display, he just won't answer it.' Specifically, Ralle means the idea of a systematic invitation system for colorectal cancer prevention – but here, too, a lot of money is involved, and the

common courage and will were apparently lacking within the medical self-government.

As a positive example, Ralle cites Holland, where early prevention of colorectal cancer is now so far advanced that a stool sample set is sent to citizens by post – with stamped self-addressed envelope included. As many as 70 percent of those contacted took part: 'Here we discuss whether a stool sample can be sent by post, and the general practitioners want it to go through them,' General Secretary Ralle said in criticism.

Immuno-oncology regains momentum

However, the medical representatives agreed that much had been achieved in the meantime regarding the differentiated treatment methods, adapted to the respective molecularly defined cancer disease subgroups: 'We have great successes in molecular research,' says Professor Bernhard Wörmann, oncologist at the Charité Hospital in Berlin, Germany. Professor Christof von Kalle, oncologist at the German Cancer Research Centre (DKFZ), also makes it clear that the 'revolution' in this field took place a few years ago – now it is a question of 'evolution', i.e. the proper application of knowledge and methods in everyday clinical practice to benefit patients.

Doctors see particular progress in breast and lung cancer, while experts diagnose gaps in brain tumours and pancreatic cancer. However, according to von Kalle, the 'revolution is inexpensive' and he calculates that

expensive, new, patented cancer drugs only account for less than one percent of health expenditure – and, development was progressing. 'Immuno-oncology has good prospects of recovery; there are more than 900 clinical studies worldwide,' von Kalle points out.

Patient orientation is in sight

The general optimism is somewhat restricted in the presentation by Professor Lena Maier-Hein, head of the department of computer-assisted medical interventions at the DKFZ. On the one hand, surgery still lacks an 'assessment culture' in Germany, is translated as: Report mistakes and learn from them. On the other hand, patient data in Germany is still not systematically brought together.

Nevertheless, she predicts further progress: 'It can be assumed that the next fundamental changes will move away from clinical intuition towards explicit, data-protected computer models, from subjective to objective decision-making.' This would enable individual treatment and ensure that the development of surgery is oriented towards patients, says Maier-Hein.

Colon cancer is successfully treated with in-patient centered oncology and prevention



Physician burnout cases are rising

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They suggest that declining per-case reimbursement has intensified radiologists' workloads leading to longer hours and greater case volume, with education and research being neglected.

Writing in the journal *Academic Radiology*, they say the issue has reached 'tipping point' with the rewards of being a radiologist outweighed by the pressures of an increasingly demanding workflow.

Meanwhile, a UK study, which analysed responses of 43,000 doctors, found that physician burnout is having devastating consequences and may jeopardise patient care. Published in *JAMA Internal Medicine*, the study – Association Between Physician Burnout and Patient Safety, Professionalism, and Patient Satisfaction: A Systematic Review and Meta-analysis – found that doctors with burnout are twice as likely to make mistakes, such as incorrect diagnoses or wrong prescriptions. Dr Maria Panagioti from The University of Manchester, who led the study, said another worrying finding was that, among junior doctors, burnout increases

the likelihood of lower professional standards by 3.5 times. That data follows a General Medical Council survey of 52,000 UK trainee doctors, which found a quarter said they felt burnt out.

Taking counter-measures

Panagioti added: 'This meta-analysis shows conclusively that the provision of safe, high quality patient care is severely compromised when doctors are physically, emotionally and mentally exhausted. Reversal of this risk has to be viewed as a fundamental healthcare policy goal across the globe.'

The causes, Panagioti pointed out, include high workload, the way teams work together and absence of measures to improve wellbeing, with doctors increasingly being asked to be superhuman.

The study team is urging the National Health Service (NHS) to rethink the environment in which doctors work, looking specifically at workload and improved teamwork.

Dr Malcolm Bell, vice chairman of the Department of Cardiovascular Medicine at Mayo Clinic, said his

organisation is taking steps toward acknowledging and addressing physician burnout with a programme of support and potential solutions. 'It's important for us to know that these phenomena are higher among physicians than other members of society. This is something we have to face up to, with work/life balance, because it can have personal and professional repercussions that will affect the individual and patient care,' Bell pointed out.

Steps contained within the Mayo Clinic Programme for Support and Solution to tackle physician burnout include: acknowledge and assess the problem; harness the power of leadership and associate it with physician well-being; improve efficiency of practice (decrease the clerical burden and explore practice redesign); develop and implement targeted interventions; cultivate community at work; promote flexibility and work/life integrations (explore reduced work hours); and promote resilience and self-care. 'We must recognise physician burnout as a moral imperative, and we must act on it,' Bell added.

Progress has been reported

e rolls

toward each tumour's individual genetic properties.

Altogether the European Medicines Agency – EMA already approved 14 new medicines for haematology and medical oncology in 2016; 19 were approved in 2017. 'That's significantly more than in other fields,' observed Dr Andreas Petzer, head of the internal oncology, haematology and gastroenterology department at the Ordensklinikum Linz, Sisters of Charity/Elisabethan Sisters, and president of the Austrian Society for Haematology and Medical Oncology (OeGHO).

Progress in basic research and, ultimately, increasingly stratified resp. personalised treatment of blood diseases and resulting solid tumours are a growing challenge. A newly developed medicine can no longer be applied globally for all patients of a certain entity.

Instead they can now only be used for patients with a carcinoma exhibiting a very specific mutation. As a rule, this patient group is only a small sub-group of all patients. 'This means that only a very specific segment of the patient pool is

suitable for testing a special medicine in clinical studies and hence comparison with the past contribution of patients per clinical test naturally will be significantly reduced,' Petzer explained.

'This implies that, as a rule, clinical research today can no longer be conducted in one centre or one country, but networked worldwide in numerous centres.'

This means that in countries with small and medium-sized hospital structures – such as in Austria – careful consideration must be given

as to which clinic or oncology centre applies for which study in order to remain interesting in the international competition as a partner for the pharmaceutical industry. If the agreed number of patients is not maintained, then, as a centre – and when this affects several centres, even as a country – one is quickly out of the race for future studies,' the Austrian cancer specialist warns, 'Therefore coordination of the clinical studies is necessary.'

To remain competitive, despite increasingly differentiated therapeutic

concepts, and to assure patients early access to innovative cancer medicines, the managing chair of the DGHO, Professor Michael Hallek, Director of Clinic One for Internal Medicine at the University Hospital Cologne, argues for a stronger integration of clinical research and patient care research in the sense of 'knowledge-generating care', where the data on therapy response, long-term outcome and undesired effects are assessed immediately. 'With this approach, every treatment is ultimately and simultaneously clinical

research too,' Hallek explains. One of the prerequisites for such a change in thinking is comprehensive patient registers that can be analysed in real time, or at least very quickly. 'That can only succeed with determined cross-institutional, intelligent and standardised digitisation of care data,' the German expert emphasised.

Such networks and registers are already being established in the United States and, according to Hallek, also ought to be implemented rapidly in Europe. ■



Georg Ralle MD is not unknown in healthcare. From 1979 to 2008, the economist worked in various leading roles, primarily for Springer Medizin Verlag and Quintessenz Verlag. Since 2011 he has worked at ICW AG, Walldorf, Hamburg, as a member of the scientific advisory board of the Medical Intelligence Service (änd). He is also co-owner of the 'Network against Colon Cancer, Munich' and Secretary General of Proventis Munich. He is a eHealth consultant at the Medicine for the Disabled Child Foundation of Charité Berlin.

Ralle made it clear that patient centering is, in part, a new achievement in surgery by talking about a surgeon who operated with a cigarette in his hand just a few decades ago. Even though such absurdities have now been banned from German operating theatres, there is still much to be done when it comes to patient-centred oncology and prevention. ■



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A thriving Czech med-tech market

The Czech Republic has a long tradition of ground-breaking medical innovations. At Medica 2018, the presence of Czech companies and traders underlined that medical devices and technologies from this country have continuing strength and value. Beate Schenk reports.



Having recorded steady growth over the past few years, the Czech medical technology sector now produces a volume of around €870 million. 13,400 people work in this field and 35 percent of the high-end products manufactured are exported. The Netherlands, Belgium, Austria and Germany are major importers of those goods.

The Czech government considers the development of new pharmaceuticals for treatment and diagnostics a priority and, over the past ten years, has provided €2.5 billion in funding to strengthen the infrastructure of the sector. This indeed has promoted the establishment of new facilities, be it hospitals, laboratories and other healthcare organisations led and financed by private investors.

According to the most recent yearbook of the Czech healthcare system, in 2016 there were 189 primary care hospitals with approximately 58,200 beds, 126 specialised clinics with 17,800 beds and roughly 27,600 out-patient facilities and doctor's offices.

In 2016, almost 2.5 million people received hospital treatment there. Roughly one sixth of all beds are operated by non-public organisations that lay great store by modern medical technology equipment.

A third of all imports originate in Germany

International manufacturers also benefit from the favourable market situation. Czechia imports a large percentage of its medical technology, above all electro-medical devices. The import volume amounts to more than €1 billion per year, including those devices that are further processed and re-exported. A large import demand is usually recorded for ventilators and orthopaedic aids but also for supplies such as syringes, needles, catheters and cannulae. Many hospitals often prefer imported goods.

Germany is the most important trading partner of Czechia and the country's most important investor, followed by Japan, South Korea and the USA. 'The Czech Republic presents itself as an attractive location for production and commissioned research and development. The evolution of the sector is facilitated by effective patent protection, the adoption of GMP, GLP and GCP standards, comparably few restrictions on genetic technology and a government that supports knowledge transfer between science and industry,' Barbora Racan Jezkova, Regional Director DACH at CzechInvest, points out.

Germany is by far the most important export market for Czech med-tech companies: 32 percent of all exports go to the neighbouring country. 'Many export-oriented Czech companies look to the

German market for their innovative healthcare solutions, from medical technology through to medical supplies and services,' adds Adam Jareš, Director of CzechTrade, the Czech Agency for the Promotion of Trade in Germany.

Both agencies act for the Czech Ministry of Trade and Industry: CzechInvest supports foreign direct investment while CzechTrade assists Czech companies wishing to expand into foreign markets.

Czech medical technology at Medica 2018

Jareš coordinated the participation of 48 Czech companies at Medica this year. Biomag presented a 3-D pulsed magnetic therapy; Eyrina introduced a semi-automatic non-mydratric fundus camera; in the Czech Republic Special Medical Technology manufactures devices for electro- and cryosurgery, with a broad range of applications in many fields; Synthesia produces naturally-based oxidised cellulose for biomedical and technical use, which is marketed under the brand name OKCEL. VUP Medical focuses on implantable and non-implantable medical devices; Watek Technology produces ultra-clean water primarily for medical, laboratory and pharmaceutical industry use.

Continuing the Republic's lengthy list, Compex/Jett Medical manufactures the first patented direct current plasma device to examine skin; Global Biomedica develops and manufactures titanium spinal and orthopaedic implants using innovative industrial 3-D printing technology; Kettex Development manufactures a video endoscope system for urological examinations; Advanced Medical Solutions develops, manufactures and sells diagnostic and therapeutic devices that include portable ultrasound and occlusion plethysmography with powerful software for arterial, venous and lymphatic diagnostics.

A history of global success

Today, few people are aware that it was a Czech, Jan Jánský, who established in 1907 the four blood



A political science graduate from the University of West Bohemia (2006), today Adam Jareš is the Director of CzechTrade, the government-run agency of the Czech Republic that promotes trade in Düsseldorf, Germany. His task is to stimulate international trade and cooperation between Czech and foreign business enterprises. Before this, he was a representative of CzechInvest in Cologne. Jareš was also an assistant member of the federal assembly in Berlin and headed the Eurocentre in Pilsen, an institution that gives out information about the structure of the European Union.

types, or that the Czech chemical scientist Otto Wichterle made the first contact lenses in 1961. Better known might be Czech scientist Antonín Holý, the first to synthesise Tenofovir, today one of the most frequently used drugs for HIV treatment and prevention.

But Czech companies hold many more records: more than 30 percent of the worldwide production of electronic microscopes are supplied by three companies in Brno: Thermo Fisher Scientific (formerly FEI), TESCAN and Delong Instruments. They benefit from the fact that today Brno is home to twelve institutes of higher learning.

Moreover, the Czech Republic is the worldwide second largest manufacturer of acute and long-term care beds. The best know medical technology company is the Czech-German Linet Group SE, headquartered in Dordrecht, Netherlands, and operating production sites in Wickede (Ruhr), Germany, and in Slany and Frycovice in the Czech Republic as well as sales organisations throughout Europe and the USA. In fiscal year 2017/18, the group generated revenues of about €252 million; with 90,000 hospital beds the company is a leading provider in Europe.

The portfolio includes acute and intensive care beds as well as beds for long-term and nursing care, gynaecology and surgery chairs. 'Linet is one of the most innovative enterprises, comparable to brands such as Ferrari or Coca-Cola,' Jareš explains, adding, 'The greater part of the production volume is exported to more than 100 countries worldwide.'

With more than 22,000 products on offer, MEDIN is one of the largest manufacturers of medical instruments in Europe. Today the portfolio covers four main product groups: traumatology, surgery, orthopaedics and dental medicine. Traumatology implants and instruments are designed for osteosynthesis in the context of severe trauma treatment.

The product range encompasses nails, plates, screws and smaller implants. An important category are patented products, the calcaneal nail C-NAIL and the OMEGA pelvic plate. The company also offers full instrument sets for certain surgical interventions. More than 50 percent of the revenue is generated by export, particularly to countries in Europe, Latin American and the Middle East.

Taiwan

Jhy-Wey Shieh sees the link between Taiwan and Germany as obvious: 'The word "trade" – of central importance for Medica – starts with "t" for Taiwan and contains "de" for Germany – there is no better way to put it.' Even though the Taiwanese ambassador's linguistic journey was not seriously intended, this year's presentation from the Taiwan External Trade Development Council (TAITRA) emphasised a strong bond between the two nations.

Report: Wolfgang Behrends

Under the banner 'Taiwan Excellence,' TAITRA arrived at Medica 2018 with a whole range of innovative medical technology – from virtual 3-D anatomical models to robotic rehabilitation helpers and smart nappies – many awarded the Taiwanese seal of approval.

'New technology can give us effective tools to deal with the challenge of people living longer,' observed Dr Dar-Bin Shieh, Deputy Minister for Science and Technology. Artificial intelligence, Big Data and personalised medicine will advance diagnostic and therapeutic opportunities – for the old as well as others – to entirely new levels,' he predicts.

VR helps body and mind

'Many people know virtual reality (VR) from movies such as "Ready Player One" or from video games. Technology here serves mainly to escape from reality – but we can also use it to solve problems in reality,' explained Lewis Chang, who introduced new products from HTC subsidiary DeepQ Technology. Known for smartphones and the VR glasses HTC Vive, the firm also provides medical technology solutions.

One of these is 3-D Organon, a three-dimensional, interactive anatomy atlas used in medical training. 'Students can move freely around an anatomical 3-D model, take it apart, layer by layer, and therefore better understand the body's spatial structures,' Chang explained. This does not replace working with real bodies, but offers an additional method to teach and learn.

The mind also can be healed via VR solutions: Oxford VR is a programme aimed to treat psychological disorders such as vertigo. 'If you can practice crossing a high bridge in the virtual

The 'mirror hand' helps stroke patients to regain hand movements by linking the healthy hand to an exoskeleton that copies movements via a sensor glove



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Presenting virtual solutions for real problems

's Medica triumphs

world you will later find it easier in reality,' Chang pointed out. In Taiwan, VR therapy is already used successfully; now the European market is to be convinced of the new technology's potential.

From huge displays to augmented reality

The Asclepus surgical table from Taiwanese company Main Orthopaedics Biotechnology also banks on the power of virtual 3-D models. On a display measuring about one by two metres, the table shows life-size bodies that move and turn freely, and can be taken apart. Next to generic body models that can, for instance, be used for trainee surgeons, patient-specific data can also be displayed, so the table can additionally be of great help with surgical planning, according to MD Min-Liang Wang, during the TAITRA presentation.

The company also produces Foresee-X smart surgical glasses, introduced last year. For 2018, Wang introduced the second generation of the mixed-reality glasses, Caduceus. 'They allow surgeons to display additional information without having to take their eyes off the patient to look at a screen,' he explained.

Support for specialists

AmCad BioMed uses ultrasound-based technology for fast and reliable diagnosis of obstructive sleep apnoea (OSA), saving patients from long-winded and unpleasant examinations in the sleep laboratory, which they then only undergo if really necessary. 'Around 25% of the adult population suffer from OSA,' said AmCad president Yili Lee. 'Some only have a mild form of the problem, which hardly affects them; others are severely impacted and treated too late because they shy away from examinations in the sleep laboratory.'

The product is reported to assist in a reliable diagnosis of OSA risk and grade within just a few minutes, with the patient being fully conscious,

3-D Organon helps medical students to understand the human body



AmCad vice president James Lee said.

Robotic hand helps stroke rehabilitation

Rehabotics Medical Technology demonstrated its 'mirror hand', a mobile exoskeleton that helps to regain motor functioning lost after a stroke. A sensor glove on the other hand records movements, which are then 'mir-

rored' by the exoskeleton, explained Rehabotics MD Jian-Jia Huang.

Many products introduced at Medica are on the brink of gaining the CE-mark, or are already available marketed in the EU. The TAITRA presentation confirmed once more that medical technology 'Made in Taiwan' is a notable force – in Europe, too.



Taiwanese firms introducing products at the TAITRA stand

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Disaster hospital gains POC ultrasound and tuition

Fulfilling a promise to Mosul

Mosul, Iraq's second largest city, is slowly rebuilding its healthcare infrastructure after years of war and destruction. Dr Henryk Pich, a consultant anaesthetist and intensive care physician at the University of Dresden, Germany, visited the region soon after the fighting had ended, supported by the independent aid organisation CADUS. Moved by the makeshift treatment centres he witnessed in hospital ruins, he promised the skeleton team of local doctors at the paediatric hospital that he would return, bringing with him much needed equipment and training resources.

When young, Dr Henryk Pich travelled widely in the Middle East and feels a personal connection to the region. After seeing the devastation caused by years of war to cities such as Mosul, he wanted to help and contacted CADUS, an independent German aid organisation building mobile clinics for areas with significant need. When the fighting ended, Pich joined a highly skilled, inter-disciplinary team of paramedics, nurses, doctors, technicians and project managers working in Mosul.

His first trip was to a refugee camp outside Mosul, providing primary healthcare to hundreds of thousands of homeless refugees. From there the team visited a specialist women and children's teaching centre, Al Khansaa Hospital, in Mosul. This formed a lasting impact on Pich: 'Al Khansaa used to be among the biggest hospitals in Northern Iraq – with 300 beds for women and children's services and a high quality reputation in the wider region. 85% of the hospital and its resources



The point-of-care equipment supplied provides many opportunities in use including focused assessment with sonography for trauma scans

critical care, time is of the essence. This ultrasound machine boots up within seconds and is ready for use straightaway.'

With ultrasound arranged, Pich had clear objectives for his next visit – to hand over the machine and, alongside an Arabic translator, deliver a training course in regional anaesthesia and emergency ultrasound. 'In Germany I carry out a lot of FAST (focused assessment with sonography for trauma) scans, and planned to teach this technique to my Iraqi colleagues, as well as lung scans and guidance for nerve blocks.'

Pich was eager to see how life had changed for the people of Mosul since his visit the previous year: 'There is some life on the streets again, security has greatly improved and, although basic materials are lacking, staff continue to work with enthusiasm and dedication. It was a pleasure to hand over the M-Turbo and deliver the training course to surgeons and radiologists. I talked about regional anaesthesia, guiding needle insertion, and how to interpret views of structures and identify nerves; I had a practice pad

and needles with me, so they could each experience a simulated exercise. One radiologist on the course was keen to use it to guide her in taking biopsies of breast tissue, an application of the device that I hadn't foreseen.

As soon as the course ended, the Iraqi attendees took the M-Turbo to the emergency room to assess a woman with an abdominal wall hernia – it was very satisfying to see it being used immediately and effectively to raise the level of care provided.'

Pich is still involved and now working with CADUS to plan ongoing support for Al Khansaa. 'It's very important to keep the connection with our Mosul colleagues, not only to encourage more donations but also to transfer knowledge and skills. I am very grateful for SonoSite's generosity. The M-Turbo was just the right piece of equipment needed. I felt a huge sense of responsibility transporting this valuable machine to a war-stricken country, for people who really needed it, but I'm very pleased with what we could accomplish. The most satisfying aspect of this experience is knowing that I fulfilled my promise to the dedicated staff at Al Khansaa. Source: Fujifilm SonoSite

Product details: eraf-sales@fujifilm.com

"I fulfilled my promise to bring resources and education that could help them deliver, and raise, the quality of care the women and children in Mosul so desperately need. Henryk Pich"

were destroyed or stolen. The staff are very well trained, but there's a lack of equipment, with a lot of improvisation and many things run at a rudimentary level. I naturally expressed my concern and desire to help and pledged to return.'

Pich is passionate about ultrasound, particularly in regional anaesthesia and emergency medicine, and uses his skills to educate others. 'Point-of-care ultrasound is a vital resource for intensivists and

emergency physicians around the world. It enables a quick and accurate diagnosis, guides life-saving interventions, and operates as the 'eyes and hands' of modern-day doctors. The reliability, durability and portability of some ultrasound systems make them ideally suited to use in war-torn destinations, and it made sense to return with an appropriate ultrasound machine and training resources.'

The potential impact of a new

point-of-care ultrasound system in the Mosul hospital could be far-reaching. Pich approached Fujifilm SonoSite for support for his return mission and a SonoSite M-Turbo system was donated. 'I know this machine well and was very happy to take it to Mosul.' Pich explained. 'It's small, light and easy to carry in one hand. It has excellent resilient and reliable probes of various types. The whole system is intuitive to use and easy to teach to others. In

Finding hidden benefits in existing solutions

A new look at closed loop stimulation

Every year of a physician's career brings new research, learning, and techniques to better save and improve patients' lives. A new year is a good time to look at existing methods and therapies with a fresh perspective. Closed Loop Stimulation (CLS) has been around for more than 20 years. Recently this demonstrated clear benefits for some patients suffering syncope (temporary loss of consciousness caused by a fall in blood pressure).

CLS is a rate-adaptive pacing algorithm – exclusive to cardiac devices from Biotronik – which works by analysing myocardial contractility, a parameter sensitive to both physical exercise and acute mental stress, whereas accelerometers only respond to physical activity.

The 2017 SPAIN study, published

in the *Journal of the American College of Cardiology*, marked the first prospective double-blind placebo-controlled trial to see if CLS yielded clinical benefits for syncope patients, given that CLS determines pacing via a physiological parameter rather than a purely physical one. It found CLS was associated with a sevenfold reduction of fainting cases in pacemaker patients – more than two decades after Biotronik originally developed the technology. 'If the findings are confirmed by larger studies, like the on-going BioSync CLS trial, it could spell a change in international guidelines to recommend CLS pacing in this patient group,' principal investigator Dr Gonzalo Baron-Esquivias said of the results.

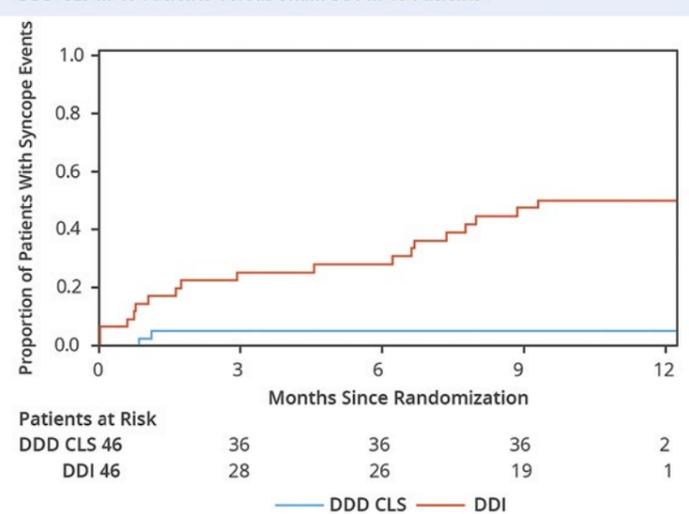
Full BioSync results aren't expected until 2022, while smaller scale studies

are giving us reasons to look again at a long-available clinical option. This year's Rattanawong et al. six-study meta-analysis – including SPAIN – found an 80 percent reduction in vasovagal syncope (VVS) cases with CLS versus conventional pacing. There are, of course, still limitations. All studies published on CLS so far have smaller sample sizes and there is as yet scarce data from patients under 40 years of age.

If a consistent clinical benefit is found across several studies for CLS – long after it was invented – how else might our patients gain from us looking for solutions using tools to which we already have access? With CLS using a physiological rather than a purely physical parameter, might it help patients suffering from atrial fibrillation or heart failure?

A new year is a good time to ask new questions. Indeed, as recent CLS data suggests, the next encouraging study result could be hiding in plain sight. Source: Biotronik

DDD-CLS in 46 Patients Versus Sham DDI in 46 Patients



Time to first recurrence of syncope per pacing mode (DDD-CLS vs. DDI) was significantly different during 11 ± 3.5 months of follow-up ($p < 0.0001$). Odds ratio: 0.11; relative risk reduction: 89% in favor of DDD-CLS; absolute risk reduction: 37%; and a number needed to treat with DDD-CLS of 2.7 to prevent 1 recurrence of syncope. DDD-CLS = dual-chamber pacemaker with closed loop stimulation; sham DDI = dual-chamber pacemaker implantation but without pacing activity; PM = pacemaker.

Contrast-enhanced ultrasound for renal masses

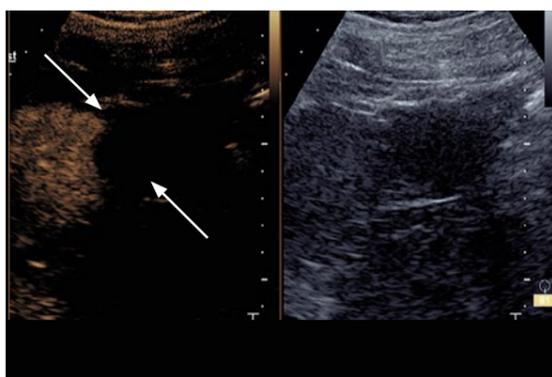
Contrast enhanced ultrasound (CEUS) has proved in trials to be more accurate than computed tomography and MRI and can help eliminate the need for unnecessary biopsies and surgery.

Led by Dr Richard Barr, Professor of Radiology at Northeast Ohio Medical University, the team has been using CEUS since 1999 and, for the specific study, focused on 721 patients referred for contrast-enhanced ultrasound (US) with 1018 indeterminate renal masses between then and 2010.

Following CEUS examinations,



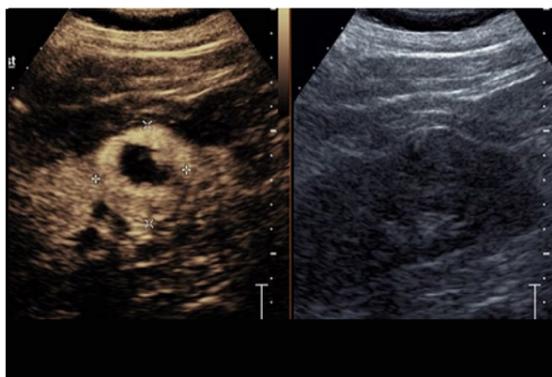
Ultrasound of the right kidney in a 65-year-old male demonstrates a solid appearing mass



After contrast injection the mass has no blood flow and is a benign complicated cyst



83-year-old male presents with bladder outlet obstruction from benign prostatic hypertrophy. On ultrasound of left kidney there is a 4.5 cm mass



On CEUS the mass (x's) is markedly enhancing more than the normal kidney. The central area of the mass does not enhance as it is necrotic. The lesion was a renal cell carcinoma.



Dr Richard Barr is President of Radiology Consultants Inc. in Ohio and a Professor of Radiology at North-eastern Ohio Medical University, Youngstown, Ohio. The research is performed at Southwoods Imaging in Youngstown, Ohio. His more than 100 scientific articles show particular interests in breast imaging, contrast-enhanced ultrasound, and elastography. He has also published two elastography books, plus several book chapters. From January, he will be the editor-in-chief of the Journal of Ultrasound in Medicine.

367 of the patients were spared biopsy, surgery or close follow-up. 'Because all malignant renal masses have blood flow, if no enhancement is present, they are benign 100%,' Barr explained.

'If we exclude vascular abnormalities and infections – usually identified clinically – most masses with

blood flow are malignant. Therefore, by using CEUS, we can confirm a mass is benign without a biopsy or surgery.'

CEUS uses liquid suspensions of biocompatible microbubbles, which are slightly smaller than red blood cells, and are injected into an arm vein during an ultrasound scan.

Each has a unique sonographic characteristic, enabling radiologists to use specific ultrasound contrast to see a contrast-only image, as well as a standard image at the same time. CEUS does not expose patients to ionising radiation and the microbubbles present no risk of kidney or liver damage.

Indeterminate renal masses are a common clinical problem with more than half of patients aged over 50 estimated to have at least one renal mass. Many renal masses are found incidentally during an imaging examination and most are benign simple cysts.

The purpose of the research,

'Evaluation of Indeterminate Renal Masses with Contrast-enhanced US: A Diagnostic Performance Study', was to determine the use of contrast material-enhanced ultrasonography in the characterisation of indeterminate renal masses.

With 100% sensitivity, the results offered a conclusion that CEUS evaluation is a highly-sensitive and specific method for characterisation of indeterminate renal masses. 'Because we can 100% confirm a lesion is benign, no surgery or biopsy is needed. That is the big benefit for patients,' Barr added. 'We have followed our first 1,018 cases now for 10 years and none of the renal masses without blood flow became malignant.'

'Also, positive patients can be treated and not watched to see if lesions grow. As for clinicians, they can be confident in the diagnosis and not have to be concerned about following up the patient.'

In terms of diagnosis, he said they can predict with high probability if a mass is benign or malignant, though acknowledged that in terms of specific diagnoses more work is needed.

Overall, the Northeast Ohio team has collected an additional 2,000 cases and is working on additional features to determine whether they can provide a histologic diagnosis of the malignancies.

'Some renal cancers are very slow growing,' Barr noted. 'If we can select these out, older patients may not need to have surgery or treatment but just be watched to make sure the lesion is not growing.'

With findings that show CEUS is a 'very robust technique with an extremely high predictive value,' Barr concluded: 'CEUS, which is available worldwide, is more accurate than CT and MRI because we have a contrast only image, so we can see very small amounts of contrast.'

'Ultrasound also has a much smaller slice thickness,' Barr pointed out, 'so we can identify 1mm enhancing nodules within a renal mass. CEUS can be used in patients with renal failure.' MN

High-quality transducers made for a few dollars

Ultrasound for budget-conscious hospitals

Engineers have developed a new high-quality ultrasound transducer that could dramatically lower the cost of ultrasound systems. The innovation – created by a team from the University of British Columbia in Vancouver, Canada – is portable, wearable and can potentially be powered by a smartphone.

Study lead, Dr Carlos Gerardo, from the university's Department of Electrical and Computer Engineering, points out that, whilst ultrasound is safe, non-invasive and the world's number one medical imaging modality, high quality hospital ultrasound systems remain expensive. 'This limits the number of machines available in a hospital and therefore creates long waiting times for patients,' he explained, 'so, we thought about a way to create high quality ultrasound transducers at a reduced price.'

Hospital ultrasound machines currently use piezoelectric crystals as their transducers – effectively small ceramic tiles which, when a voltage is applied to them, expand and contract, generating ultrasound waves.

'Conversely, these piezoelectric crystals generate electrical voltages when they are squeezed by external ultrasound waves; these voltages are then read by a computer and an

image is displayed on a computer screen,' Gerardo explained. 'For our research, we replaced the traditional piezoelectric transducers with new drum-based CMUT technology using low-cost materials. This resulted in a simple fabrication process to create high-quality transducers for only a few dollars.'

Transducer drums have typically been made out of rigid silicon materials that require costly, environment-controlled manufacturing processes.



Dr Carlos Gerardo, postdoctoral researcher specialising in MEMS-based ultrasound transducers for biomedical applications at the Department of Electrical and Computer Engineering, University of British Columbia, in Vancouver, Canada.

However, the high manufacturing costs of CMUTs has been countered by the researchers by the use of plastic-like materials instead of semiconductors.

Gerardo explained that, by using a photosensitive polymer resin called SU-8, with fewer fabrication steps, the cost was dramatically reduced, and with the added bonus that the plastic-like materials actually boosted the device sensitivity. 'This enabled the creation of high-quality ultrasound transducers for biomedical application at very low costs,' he pointed out.

'Our technology uses tiny vibrating drums made of polymers (poly-CMUTs), each with a diameter of around 1/10th of a millimetre. We have thousands of these drums in our transducer that vibrate at the same time and produce ultrasound waves.'

'The benefit for the medical field is that this technology has the potential to reduce the current cost of ultrasound machines used in hospitals. If the cost of the machine is reduced, then a hospital can afford to buy more ultrasound systems and reduce the waiting times for patients.' MN



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New guidelines for arthroplasty

Joint efforts: knees

Report: Anja Behringer

According to the Swedish Knee Arthroplasty Register, knee arthroplasty – with a revision rate of five percent after ten years – is one of the most successful surgical interventions of the post-World War II decades.

The most frequent reasons for revision are loosening or infections, whereas patient dissatisfaction is often caused by mobility impairment and pain. Since many adverse events are associated with existing co-morbidities, the German Society for Endoprosthetics (AE) demands better patient information prior to surgery. Particularly, risks and benefits need to be more thoroughly discussed and unrealistic patient expectations regarding the implant need to be dampened.

Individual risks include infections, obesity, neurological disorders and other diseases. The psychological status of patients must also be considered, since depression, for example, can lead to frustration about slow healing or the situation in general. Moreover, cultural and social factors, such as a patient's age and health status, can influence outcomes, says Professor Dr Karl-Dieter Heller, Medical Director of the Orthopaedic Clinic at Herzogin Elisabeth Hospital in Braunschweig, Germany, and Secretary General of AE. 'The rule of thumb is: The better mobility and function are prior to surgery the better the outcomes.'

Too many surgeries?

Before arthroplasty is considered, all other therapy options should be exhausted: 'Even when the X-ray shows severe arthritis, but the patient's mobility is only slightly impaired and the patient is not in pain, we won't perform surgery! About a third of patients referred to us for surgery are sent home, because we don't consider an arthroplasty necessary. In real orthopaedic life, a fraction of patients with knee problems undergo arthroplasty –



Around 187,000 patients in Germany received a knee replacement in 2016



All therapy options should be exhausted before arthroplasty is considered

the first line treatment is conservation, i.e. joint-saving therapies,' Heller points out. He recommends patience: 'After surgery the healing process takes about half a year, after that the body should have become used to the implant.' How long it

will take to regain mobility and freedom from pain differs widely from patient to patient.

Moreover, the healing process of hip and knee replacements are very different: A patient who received a new hip can move pretty well after two days, while a knee implant requires the patient to muster dedication and discipline throughout the



Defective implants are replaced by revision models

physio-therapy phase.

In view of the fact that in time to come there won't be a remedy for arthritis, endoprostheses play a major role. Nevertheless, for elderly patients being mobile is crucial for their overall health status.

Recent studies indicate that arthritis-induced immobility is associated with a 40 percent increase in the risk of myocardial infarction compared to post-surgery activity. Lack of activity causes muscle atrophy – a serious problem according to Heller. To maintain mobility the pros and cons of conservative treatment, such as pain management and physiotherapy and, also, arthroplasty, need to be determined. The right decision for each individual can only be the result of an intensive communication process between physician and patient. After all, the knee is a highly complex anatomy and regaining its function is time-consuming.

New guidelines for the 'forgotten knee'

These issues are addressed in guidelines on knee replacements, published by AE in late 2017. The recommendations on indication encompass primary and secondary criteria that aim to objectivise a patient's subjective experience of pain and to include the patient in the decision-making process. Any discussion on volumes and quality needs to consider indications.

In 2016 around 187,000 patients received a knee implant. Heller recommends selecting the orthopaedic surgeon carefully. In certified hospitals a surgeon has to perform a minimum of 50 implants per year. According to the guidelines, replacement surgery is indicated when 'the knee is visibly damaged or the patient has been suffering from unbearable pain for three months'.

The arthroplasty patient also should be aware that s/he will not be able to follow a usual daily routine for up to three months and full rehabilitation may take up to two years, and also that s/he must be prepared to contribute to healing by complying with behavioural requirements. Since pain and impairment of mobility are subjective factors and culturally influenced and, since not every patient is fully aware of the risks involved in surgery, patients evaluate the outcomes very differently.

One of the, albeit rare, post-surgery adverse events is implant loosening. Infections and instability

A focus on endoscopy

Through the keyhole or open s

Physicians in Germany remove around 200,000 gall bladders annually, mostly by minimally invasive surgery, the so-called keyhole surgery. While gall bladders and appendices can be removed through a tiny aperture in the body, large tumours cannot.

Small cuts, less blood loss, fast mobilisation

Patients also profit from the keyhole technique with joint and bone problems in the knee, shoulder or elbow. Advantages: small cuts, less blood loss, fast mobilisation, altogether a lower operating risk, especially for older patients.

By means of a five-fold magnification and very high resolution of the mini-camera on the endoscope, this procedure offers high accuracy in the anatomical view and protection of organs, vessels and nerves in the abdominal space.

Visceral surgery particularly ben-

efits from the technique, which triggered great euphoria when introduced into medicine over two decades ago. Nonetheless, it has not replaced open surgery in certain fields, as a comparison with practice elsewhere shows. According to current statistics presented by Professor Ayman Agha MD, chief physician in the Clinic for General, Visceral, Endocrine and minimally invasive surgery at Munich-Bogenhausen, this is the case for minimally invasive (laparoscopic) surgery for colorectal cancer.

The procedure is used in about half of the United Kingdom's cases, and, in percentages, 90 percent in Denmark, 80 percent in the Netherlands whilst, in Germany less than a third of cases involve laparoscopic surgery.

Although current evidence for both procedures shows them to be equivalent and even indicates advantages for laparoscopy, Agha



sees the following reasons behind European differences:

- MIS to treat colorectal cancer is a genuinely technical challenge for many surgeons.
- The surgeon's age plays a deci-

sive role: Older physicians prefer proven common surgical methods for colorectal cancer, whereas surgeons are open to new and innovative techniques.

- Much practice is needed to mas-

ter this technique – a specialist expertise gained from performing many demanding operations.

For over 16 years Agha has led and supported clinical research projects in colorectal and endocrine MIS and he uses laparoscopy in 95 percent of rectal cancer operations.

In the '90s, when minimally invasive surgery (MIS) arrived, it was feared that malignant colon and rectal carcinomas could not be removed hygienically and patient survival would be jeopardised. Meanwhile several large-scale international studies rebutted those reservations. In terms of long-term outcome after MIS, many patients are at least as likely to survive as after open surgery. The relapse quota for a malignant tumour is still at least the same for both.

Nevertheless, for chronically inflamed intestinal illnesses, Agha believes that the decision on which surgical method to use should

Effective wound care

Healing helped by fish skin or bio-ink



Professor Karl-Dieter Heller MD studied medicine in Aachen, Germany, and London, UK, in 1983. Following completion of his habilitation, in 1997 he received the *venia legendi* in orthopaedics from Rheinisch-Westfälische Technische Hochschule Aachen. He was appointed medical director of the Orthopaedic Clinic in Braunschweig in 2000 and has been secretary general of the German Society for Endoprosthetics (AE) since 2015. In 2016 Heller became a founding member and vice president of the German Hip Society (DHG). His awards and honours are numerous and he is active in several surgery and orthopaedic as well as professional organisations.

and pain behind the patella, or frontal knee pain, occur more frequently and might indicate an incorrectly positioned implant or incorrect ligament alignment during surgery. In any case, the causes have to be ascertained.

Increased risk of implant failure is also associated with obesity and comorbidities such as gout, diabetes, rheumatism and neurological disorders such as Parkinson's disease. Moreover chronic infections, e.g. of bladder or teeth need to be cured before surgery, because bacteria can spread and infect the implant.

Today, infections are considered the major risk in arthroplasty. If a patient turns out to carry an infection prior to surgery, the intervention is postponed. 'Infections are a serious adverse event in only about one percent of initial implantations. However, in revision, and above all tumour arthroplasty, the infection rate is significantly higher,' Heller points out. Fortunately, silver-coated replacement joints can reduce the infection rate.

Many methods to treat current or chronic wounds are available. However, the differences in general conditions prevailing in hospital, or for out-patient care, make effective therapy more difficult. Each patient also has other preconditions for healing. Improved communication between everyone involved in the treatment would benefit patients. We see a lot of progress with the issue of 'wounds,' physician Professor Bert Reichert explained, 'but also simply insurmountable obstacles.'

Reichert, who is medical director of the Clinic for Plastic, Reconstructive and Hand Surgery, Centre for Serious Burn Victims at the Paracelsus Private Medical University hospital in Nuremberg, heads the conference at the first Nuremberg Wound Congress.

For him, it is particularly important that not only the medical specialties but the various professional groups who deal with wound care are brought together so that each can develop a precise notion of what the others actually do with a patient.

Innovations in wound treatment

Wound applications made with fish skin, cold plasma, and stem cells from perspiratory glands – what really helps with open wounds? 40,000 amputations annually result from chronic wounds that just won't heal despite complex, interdisciplinary therapy. The body is unable to close them after months or even years. Such permanently open areas are usually caused by diseased veins and arteries, diabetes or tumours.

Pain, itching, moisture and unpleasant odours enormously restrict the life quality of those affected.

Innovative therapeutic approaches include obtaining stem cells from the patient's own fat or perspiratory glands in underarm skin, and a vacuum sealing therapy in which fluid is sucked from airtight packed

open wounds, thus promoting the circulation in the surrounding tissue and stimulating skin growth. Cold atmospheric plasma, an ionised gas, can favour wound healing by substantially reducing even multi-resistant pathogens.

An acellular matrix made of fish skin is considered a new generation among wound applications, which, in first use, has even healed treatment-resistant wounds. The product is obtained from the skin of the Atlantic cod, or its subspecies, found north of Iceland. With the animal cells removed, the tissue matrix is placed on the open area, where it forms a mesh along which human skin cells can locate, divide and grow.

Finally, a functional, vital tissue is created here.

Additionally, omega 3 fatty acids contained in the fish skin appear to favour wound healing.

Their infection-impeding, antibacterial and antiviral effects have been proved in the laboratory. Thus amazing successes with it have been achieved recently in clinics. In clinical studies the method has proved its quality and effectiveness, and even superiority compared to common wound applications.

'When looking at the seemingly expensive modern methods,' Reichert observed, 'one ought not to forget that classical bandage changes occur more frequently and therefore a longer healing time also induces considerable costs.'

Also among much discussed alternatives for chronic wound treatment are transplant materials made of animal tissue, which, as new generation wound applications, might enrich the sometimes-confusing market.

Finally, physicians in Spain are raising eyebrows among specialists with the bio-ink from the 3-D printer. The so-called bio-printer can form new tissue with its ink containing collages and fibrin, thus closing even deep wounds. Such a 3-D print treatment ought not to take more than two minutes. 'Innovations always stimulate curiosity,' the Nuremberg wound specialist said, 'because, until now, it's been impossible to heal patients with chronic wounds completely, even if alternative methods at least bring relief.'

With the Nuremberg Wound Congress, Reichert hopes to draw on past traditions. Similar events have been held in the South German region in previous years, but recently have been absent. The subject 'wound' is far too important in his opinion not to seek exchange with adjacent disciplines, beyond the techniques of one's own specialty, and to continue education. There has been no trans-regional forum beyond isolated regional initiatives.

Progress can be seen in the most diverse range of wound treatment, as



Professor Bert Reichert, who gained his doctorate in 1984, was appointed chief physician of the Clinic for Plastic, Reconstructive and Hand Surgery, Centre for Serious Burn Victims at the Paracelsus Private Medical University, Nuremberg, in 2004. At the same time as he began his professorship there, in 2014 he became director of the university hospital.

well as in the qualification of medical specialist professions and efforts to develop guidelines. In contrast everyday experience impedes unabated the fact that there are completely different framework conditions for treatment of people in hospital and out-patient care.

Thus, for instance, forms of wound treatment commenced in a hospital often cannot be continued as an out-patient by consulting physicians. Add to that the differences between the patients insured by the state and those insured privately. In the state health insurance plan, the efficiency rule applies, which always asks: What is necessary, appropriate and economical? Speaking of negative pressure therapy, Reichert explained: 'There are institutes that test whether a treatment method is so convincing that one cannot deny it to the patient, and health insurers are obliged to absorb the costs. For decades these investigations are unanswered, for example for negative pressure therapy, because the research study situation is difficult.'

'On the other hand, we know that in hospital, simply from experience, how good the treatment is. And we would want to have it for patients in the out-patient segment. However this is only possible as an exception after case-by-case review.'

The Wound Board at the hospital's Wound Centre deals with these problems in regular discussions, following the precedent of the interdisciplinary tumour board. It is unusual, but of decisive importance to ask dermatologists, vascular surgeons, trauma surgeons or plastic surgeons to give advice on wound treatment.

Age is a risk factor

Age is the largest risk factor for chronic wounds. Four million people in Germany suffer today from such wounds and there will be more in the future. Health and youth is a transitory condition. Therefore preventive education is necessary about which illnesses, for example, can be avoided by proper diet and exercise.

Diabetes patients need nutrition advice as well as training about how to avoid injuries to the feet through minor injuries due to loss of sensitivity and thus prevent serious complications such as amputations.

Sick people with chronic wounds have to learn to care for themselves, which is why wound treatment needs more education and public attention in all its aspects. AB



urgery?

depend on whether patients have a benign or malignant illness – because tumour size and location (whether colon or rectum) and a patient's body-mass index play a decisive role.

Minimally invasive surgery limitations in techniques

Despite rapid MIS development in recent years and especially outstanding technical equipment, the question arises as to whether there are limits to MIS techniques. Although MIS is performed, common open surgery is still the standard procedure e.g. for large liver resections. In Agha's opinion this also applies to large pancreatic or head tumours. By contrast, MIS can be applied with good results to benign and malignant pancreatic carcinomas found at the tail of the pancreas.

Much operating experience is necessary to perform successful keyhole surgery. Significantly more time is

needed for minimally invasive interventions than open surgery.

The German Society for General and Visceral Surgery offers a certification process whereby physicians must document a minimum number of operations.

After more than 20 years of experience it is pretty clear when the procedure is suitable and when it is better to operate using conventional methods. In some cases the MIS has disadvantages that cannot be overlooked, e.g. if earlier interventions left very large scars in the abdomen or if, in a complex cancer operation, several abdominal organs are affected.

Technological progress eases the work of physicians with the use of ever-smaller instruments. The modern devices are only millimetres in size. In particular, the optics have improved enormously, delivering razor-sharp images of the body's interior to high-resolution monitors. In addition, the 3-D technology shortens the learning phase for new physicians. AB



Professor Ayman Agha MD has been head physician in the Clinic for General, Visceral, Vascular and Thoracic Surgery at the Munich-Bogenhausen Hospital since 2014. Born in Gaza, he gained his German school-leaving certificate at the University of Bonn in 1987 and took his state exams at the University of Erlangen-Nuremberg in 1993. At the Clinic and Polyclinic for Surgery at the University Hospital Regensburg, he became senior physician in 2000. His clinical focuses are cancer and visceral surgery, minimally-invasive surgery as well as chronically infected intestinal illnesses and endocrine surgery. As a researcher he supervises and supports mainly clinical research projects in minimally invasive colorectal and endocrine surgery.

Junior radiologists must learn about intelligent tools

The dawn rises over information specialists

Recent developments in artificial intelligence (AI) created a veritable hype. However, that initial awe was increasingly mixed with apprehension about the potential effects of AI on healthcare. In radiology bleak dystopias are conjured up with AI replacing the human radiologist. A scenario that Dr Felix Nensa, consultant at the Institute of Diagnostic and Interventional Radiology and Neuroradiology at University Essen, Germany, considers premature to say the least. 'Artificial intelligence will not replace the radiologist,' he told European Hospital correspondent Sascha Keutel, adding: 'Rather, radiologists who do not use AI will be replaced by those who do.'

Deep Learning as an AI method is developing swiftly and today offers a

superior approach to medical image analysis. In radiology it has become indispensable. Nevertheless the use of AI is under scrutiny and often the question arises: 'Should we be scared of AI?' But 'Who are "we"?' asks Nensa, and points out that the use of AI will have a different impact on different actors in healthcare.

Man and machine – a powerful team

Over recent years, data volumes in radiology, particularly in multi-slice imaging, have exploded. Radiology facilities would profit immensely from systems that can read multi-slice images quickly. 'Radiologists are comparatively expensive specialists but, after all, they are human beings. AI applications can take over tedious

tasks, such as counting and measuring metastases and/or enhance the diagnostic precision of such tasks. In the end the patients will benefit,' Nensa points out, adding: 'For our society that would be a great success, because it would mean better and maybe even cheaper healthcare.'

However, such benefits can only be realised with physicians who do not feel threatened by these developments and accept AI in their daily routine. 'Obviously the ways radiologists work will change. AI will definitely become part of our professional life, for example to diagnose simple cases or to perform repetitive tasks,' Nensa predicts. There is no reason to feel threatened, he underlines, because after all the tasks of a radiologist involve far more than

reading images. Radiologists work on tumour boards, they treat diseases, e.g. with local ablations or interventional radiology, they arrive at diagnoses by analysing images and the medical history of patients and they talk to patients. 'These are all activities that are not easily automated. Thus, neither radiologists nor specialist physicians in other disciplines need to be worried about their job.'

Nensa compares the situation to the introduction of autopilot systems in aviation: The technology did not replace human pilots but expanded their job description. If an airport is adequately equipped, aircraft can take off and land autonomously. 'But honestly, who would dare take a plane without a pilot?' Nensa asks. 'AI is helpful when it comes to procedures that have been learned and practised thousands of times. But the moment something unexpected happens it's by no means certain that an AI system will take the right decision. You remember the pilot a few years ago who landed his plane on the Hudson River? Would an autopilot system have been able to do this? Most certainly not!'

How will AI affect diagnostics, treatment and workflow? 'I venture a guess that, in the long run, the diagnostic disciplines will move closer together. It's been predicted before that radiologists and pathologists will evolve into information specialists. This will also hold true for lab and nuclear medicine to the extent that they are involved in diagnostics.



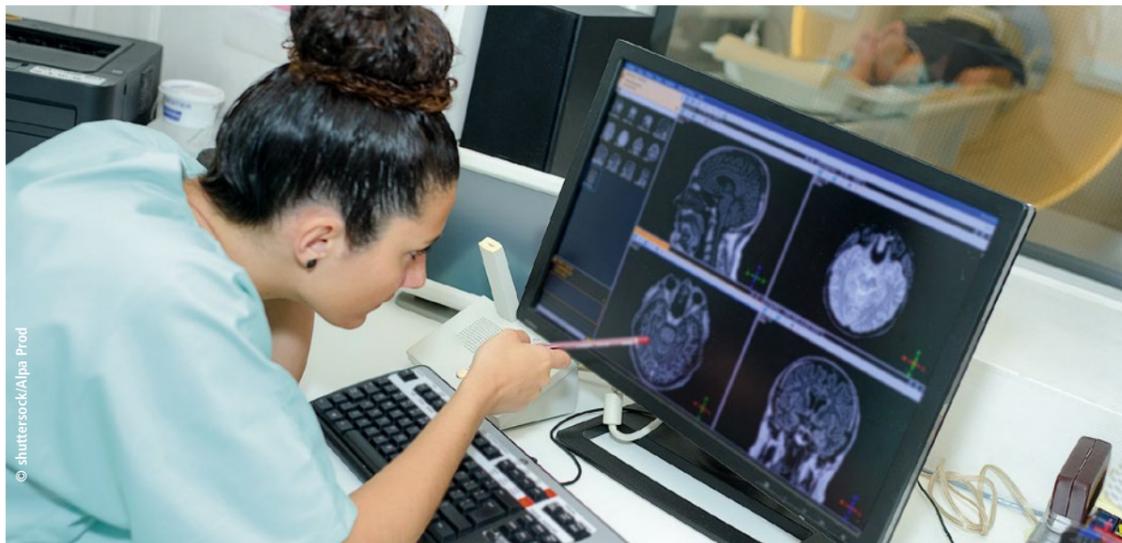
Dr Felix Nensa is a consultant at the Institute of Diagnostic and Interventional Radiology and Neuroradiology at University Essen in Germany. Before entering university, he worked as a freelance developer for the Research Institute for Diagnosis and Treatment of Early Lung Cancer at Augusta Hospital, Bochum, where he wrote a diagnostic software program for automated sputum cytometry. Nensa enrolled in a distance learning program in computer science when undertaking his medical studies at Ruhr University Bochum.

Such a clinical information specialist will be in charge of diagnostics and cover all these areas. Consequently, specialists in other areas will focus on therapy.'

The curriculum must adapt

The role of AI instruments in radiology is hotly debated – which has led to statements such as the one in by Geoffrey Hinton in 2016, that the radiologist training should be stopped immediately. 'I most strongly disagree. I'm entirely convinced that, in 2021, we will need even more radiologists than are currently in training.'

Nonetheless, Nensa urges that the curriculum be revamped. 'New training programs have to prepare medical students for this new reality. We need to teach junior radiologists how intelligent tools work and how these tools can help improve healthcare, and how radiologists effectively monitor the application of these tools.'



AI in medical imaging:

Rads must control their own destiny

Radiologists have not ended talk about artificial intelligence and machine learning but, rather than fear for the future of their profession, they themselves must decide how that should be, an eminent expert Dr Woojin Kim warned ECR 2018 delegates in Vienna in May.

Two years in discussion and the hype around artificial intelligence (AI) is far from fading. Interest has never been higher, and the number of people exploring machine learning (ML) is at its peak.

Media bombing, notably on advances in computer vision using deep learning in machine v. human imaging challenges, have fed the beast. 'We've read a lot of articles on the topic. Since 2015 machines have been doing better than humans at certain image detection and classification tasks,' said Woojin Kim, Chief Medical Information Officer for Nuance's healthcare division in Los Angeles, California, USA.

However, the machine still needs the human, and not only in radiology. Slight street sign modifications have shown that you can completely fool ML algorithms. Twitter notoriously taught the Microsoft AI

Chatbot to become a 'racist asshole,' highlighting a bias problem when it comes to AI.

These failings emphasise the need for proper arbitrage when using this technology, Kim insisted. 'There are tremendous advances in AI but you really need to incorporate the domain expertise that comes from us into this technology, otherwise you cannot read everything,' the expert advised.

Trusting machines

The black box problem is real and size won't really solve anything. IBM Watson reportedly decided to give contrast in error. With a 29.9 confidence level the machine wanted to administer contrast to a patient on haemodialysis with end-stage renal disease. 'Some people don't think this is a problem, because they say they have the biggest black box. My

question to you is, would you trust this machine to protocol all your patients without any human intervention, knowing that it can make mistakes like this? Those are some of the things you want to keep in mind and think about,' Kim warned.

The world's smartest leaders have thought of what ML would bring to the world. But history shows that one should be careful with these kinds of predictions. 'We all remember the X-ray hoax by Lord Kelvin back in the late 1890s,' he recalled. 'We can learn a lot from history, also when it comes to AI.'

New technologies can certainly eliminate jobs; they can also create new demand for products and services. 'For example ATMs do a lot of things that a bank clerk does, but if you look at bank statistics, we have more bank holders today than ever,' said Kim, adding that humans

have this unique ability to create use over value.

Taking control

Instead of thinking of what 2025 will look like, radiologists should think of what it should look like, he suggested. 'Some of the changes are going to be happening fast. Some will use algorithms that can really outdo human performances. But a lot of these processes are going to be a lot slower than you think, and a lot of these will turn out to be just hype.'

In addition, a lot of factors remain beyond anyone's control, and they will limit the adoption of AI technology in medical imaging.

Nonetheless, some people tend to have tunnel vision, which narrows down the scope of potential AI applications in radiology. 'When you look at all the papers out there, you see everybody focuses on using AI to make a finding. But that is, and I want to challenge all of us here, why don't we do peer reviews?



Because we do so much more than just make findings as radiologists,' he said.

By 2025, radiologists could really have AI to impact on every aspect

Extracting morphology, texture, function, metabolism parameters

Radiomics will transform tumour characterisation

Tumours change over time – and not only in size. They also evolve genetically, mutate and spread through equally diverse metastases. Each is unique and present with a more or less complex structure, but rarely as a unified entity. Characterising them from A to Z and from detection to neutralisation remains a challenge for modern medicine. Radiomics could be a powerful ally to assess tumour heterogeneity and replace the invasive and insufficient methods that are currently used, according to prominent French radiologist who spoke during the last meeting of the European Society of Urogenital Radiology.

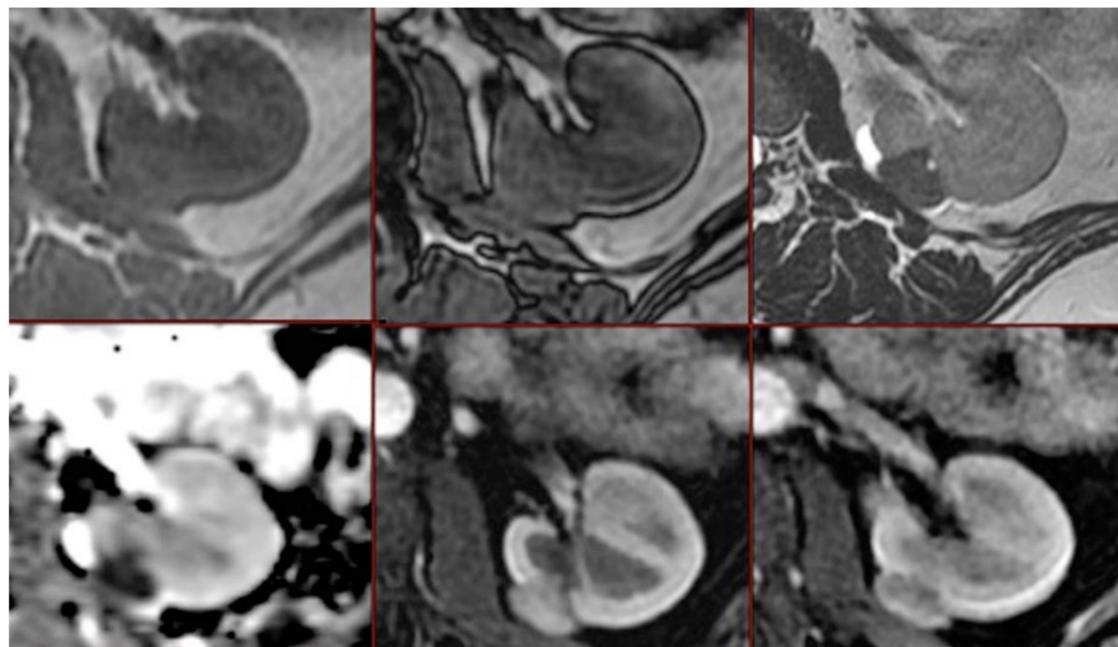
Report: Melisande Rouger

Physicians are still limited when it comes to assessing tumour heterogeneity in terms of phenotypes or genotypes. The methods that are currently used in reference centres to that purpose are mainly to perform biopsies at 5 or 6 different sites of the tumour. Not only are these methods invasive, they are also limited over time, according to Nicolas Grenier, head of urogenital and vascular radiology at Pellegrin University Hospital in Bordeaux.

'These methods just provide useful information for tumour mapping, but they do not enable assessment of tumour evolution over time with gene expression modifications, or to spot new localisations, i.e. metastases,' Grenier said.

Tumours do not have a permanent state and there may be more than one story within the same lesion. 'Within the same tumour you may have different fragments that do not have the same severity, or the same genes or expression factors. You can have mutations in all the cells or just in a few regions,' Grenier said.

Over time, the tumour may spread through metastases, which may also not have the same phenotypes. Depending on their location in the body, these new lesions may present very distinct phenotype expression.



Example of mpMRI of kidney tumours: Diagnosis of poor-fat angiomyolipoma is based on the association of a low signal on T-2, a low ADC, a high wash-in and a high wash-out after contrast. This diagnosis is impossible using ultrasound and CT alone

Radiomics could help solve tumour heterogeneity problems with the passing of time. The whole idea behind radiomics is to extract parameters on morphology, texture, function or metabolism, which enable characterisation of the entire tumour and its corresponding metastases. These parameters, or descriptors, once correlated with

genotypes, or clinical or treatment response data, can give a full picture of both spatial and temporal tumour heterogeneity and provide prognosis prediction.

However, to implement this game-changing approach, we need to review the way we perform scientific research completely, Grenier stressed. 'We are still following

Descartes' principle and start with a hypothesis to build an entire protocol, which is supposed to confirm or infirm that hypothesis. To work with radiomics, we must do the exact opposite, i.e. screen an entire population to extract descriptors, to formulate a hypothesis, for instance which population may be more receptive to a given treatment,' he said.

In the end, radiomics works a little like genomics, in which genes are extracted from a population cohort to determine which groups have which genome, information that can help assess who will better respond to a particular treatment.

Artificial intelligence (AI) will provide the horsepower that is needed to mine and select meaningful data generated by algorithms. These algorithms extract thousands and thousands of data, and AI can help sort out the most interesting and pertinent of these, which, once correlated to genetic or clinical information, will help advance our research.

'AI will also save time and expedite work by taking care of simple but repetitive tasks, enabling physicians to focus on more interesting parts of their jobs,' Grenier added.



Diagnostic radiologist Dr Woojin Kim is Chief Medical Information Officer (CMIO) at Nuance Communications Healthcare Division and a musculoskeletal radiologist in Los Angeles, USA. An entrepreneur, he co-founded and was Director of Innovation at Montage Healthcare Solutions, which was acquired by Nuance in 2016. Other interests: Big data, health IT, mobile health, global health, telemedicine/teleradiology, wearable technology, and machine learning/deep learning.

the UK and the USA, or radiologists experiencing tremendous levels of burnout,' he suggested.

An ability to adopt novel technologies

Radiology has been traditionally very good at adopting new technologies and incorporating these in daily workflow.

'I'd like to shift current focus and think of how we can use this methodology to mitigate the negative impact and emphasise the positive potential,' Kim concluded. MR



Nicolas Grenier is a professor of radiology and head of urogenital and vascular radiology at Pellegrin University Hospital in Bordeaux, France, where he also coordinates the radiology and nuclear medicine departments.

Nonetheless, radiologists must keep an eye on the quality of data extracted by machines, to ensure images are free of artefacts, noise and movement, and simply good enough to work with, he insisted. 'The imager's eye is important in quality control, and also to ensure that the data remains pertinent within the context.'

Research with radiomics in kidney tumour is just beginning, with less than 10 publications so far, each focusing on a particular aspect of the field; for instance using CT to extract purely morphological parameters for treatment response, collecting functional parameters based on MR PET to correlate with tumour grade information, etc.

'All these studies are experimental and carried out at a single centre. Besides, most studies have a commercial purpose and aim to determine which is the most appropriate algorithm for which context in order to sell it. We have nothing really practical so far. We'll have to sort out the results and compare experience,' Grenier pointed out.

Pellegrin Hospital has a few initiatives underway using AI, notably in cardiac arrhythmia and stroke, and has just started a project to develop radiomics in oncology, in cooperation with Sophia Genetics and local radiology teams including the Bergonié Cancer Institute.

Grenier and his colleagues are working with what he called pre-radiomics, i.e. multiparametric MRI in kidney tumour, with encouraging results. 'We can now describe the tumour histological type based on MRI sequences, something that was only possible through biopsy before.'

Radiomics will enable things to advance further, notably by classifying tumour types and grades, determine which part of a tumour has the highest grade, and assessing early treatment response for instance in metastatic cancer using anti-angiogenic therapy, he concluded.



of the healthcare value chain, and help clinicians make better decisions. 'AI could help with scheduling, protocols, workflow, making actual reports, communication fol-

low up and patient safety. I think there's a tremendous potential for AI in our field and I really want to see AI affecting problems that we have, such as workflow issues in



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Qualitatively high-value analysis: cheaper in the end

LC-MS in clinical diagnostics

In past issues of *European Hospital* repeated attention was drawn to developments in the clinical application of mass spectrometry-based methods in patient care. Various aspects became significant.

Report: Walter Depner

Value of methods

Today the use of Liquid Chromatography Triple Quad Mass Spectrometry (LC-MS/MS) for therapeutic drug monitoring (TDM) can be considered today's standard, although classically applied immunoassays continue to be practical. However, the limitations of these techniques, e.g. non-specificity and matrix influences have immediate impact on therapy decisions. Misjudgements have fatal consequences. This raises the question whether this can still be tolerated today.

In combination with steroid analysis, the inadequacies of ligand assays due to cross reactivities among many structure homologues have been known for a long time. That is why in many areas mass spectrometry based procedures have been available for the broad routines for years or have replaced ligand assays.

Generating parameter profiles in mass spectrometric procedures

For historical reasons, clinical physicians think frequently in single parameters. The exceptions are haematological diagnostics (haemograms), electrophoresis or lymphocyte differentiation, where parameter profiles are used for interpretation. With the mass spectrometric procedures, parameter profiles can be generated without a great deal of additional effort, already used for example, in steroid analysis and metabolomics. Here more rethinking is necessary. Professor Uta Ceglarek from Leipzig has already pointed to the advantages, namely smaller sample volumes, simultaneous analysis, and the absence of cross reactivities.

Dr Kromidas emphasised the progress with REIMS (Rapid Evaporative Ionisation-MS) in cancer surgery, thus the surgeon learns something about whether the tissue is benign or malignant in real time.

Another revolutionary advance has resulted from the use of MALDI-TOF fingerprinting for sequence identification, a technique that has become indispensable in the laboratory.

Technical aspects

Meanwhile the sensitivity and robustness of current LC-Tandem-MS systems has reached a degree that allows robust measurement of

many medically relevant parameters, e.g. biogenic amines, steroids, vitamins and metabolites.

The restriction lies in the lack of fully automated random access systems, such as those familiar for clinical chemical or ligand assay based analysers. Even if the external laboratory is less affected than the hospital laboratory, there are also various approaches to closing this gap.

One way is the special 'front ends' meanwhile available, compatible with the LC/MS coupling: open systems that permit in-house development sample by sample rather than the batch processing. In the case of hospital patient care some parameters are desired potentially 24/7, e.g. TMD, which can be accomplished with such systems.

Also, the first fully automated systems have been launched in the market. However, as closed systems they only provide procedures that the manufacturer considers interesting and offers. Together with available KIT methods, users lacking methodical experience also have the opportunity to apply MS based procedures.

Sample preparation and LIMS connectivity

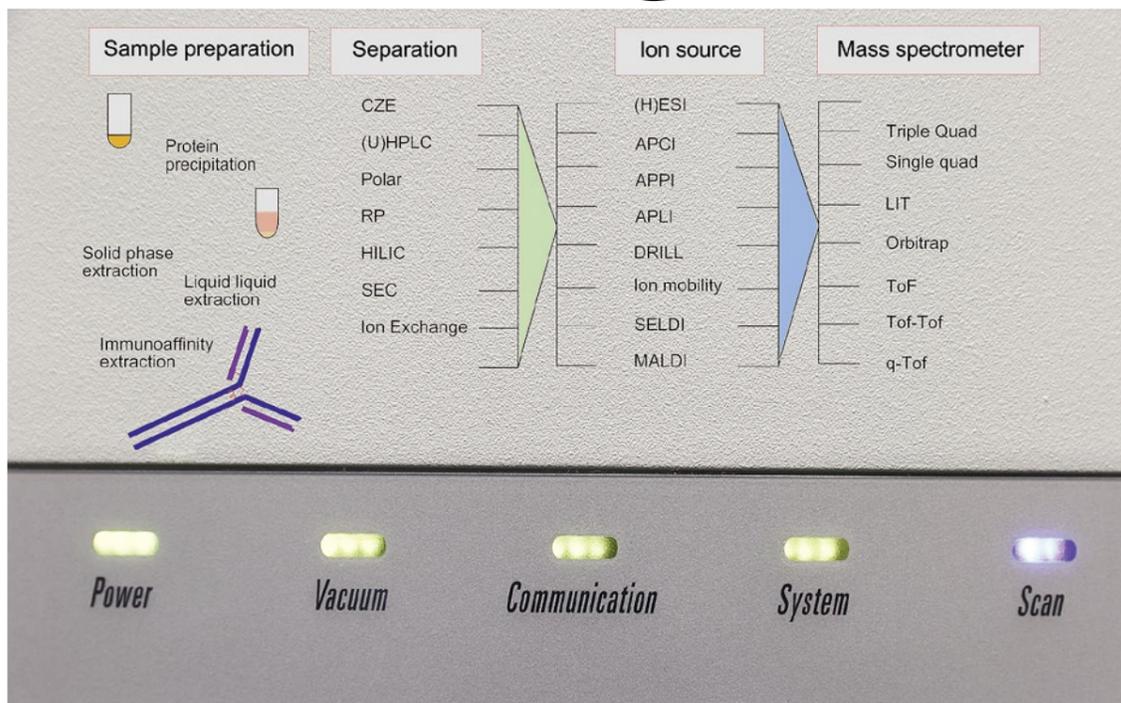
Dr Thomas Stimpfl, from Vienna, gave special attention to aspects such as sample preparation and LIMS connectivity. These features are normal in commercial, fully integrated analysers. Increasingly they are introduced even with in-house systems and contribute substantial error reduction and time saving compared to the manual method.

The advantage of a fully integrated system is that the manufacturers can match the individual components optimally, so that space-saving systems are also possible in the random access modus. Such developments are also conceivable in-house. As of yet it is impossible to anticipate the down times and MTBFs with fully integrated systems.

Advances in the development of ion sources, e.g. DRILL technology lead to 10-fold increases in sensitivity. Coupling with ion mobility separation is suitable for suppression of isobar interference and thus delivers



Close-ups from the APCI source.



improved specificity.

The application of immunoaffinity purification in the context of sample preparation for LCMS ought to permit an up to 1000-fold enhancement of the peptide target. That could mean the use of a stable isotope marked internal standard to improve reproducibility.

Even the determination of enzyme activity, by measuring the substrate, can be done sensibly using LC-MS/MS. In the laboratory of Prof Brian Kevil in Manchester the renin activity is determined routinely with LC-MS/MS.

The wide range of high-resolution mass spectrometers permits use for database searches and identity confirmation of analytes as well as separation from interferences, whereby compromises in sensitivity are needed here.

Current and future medical aspects

Our own data indicates, for example, that testosterone in women with an automated immunoassay deviates within a range from -80% to +80% from the LC-MS/MS measurement, whereby the overall error for LC-MS results is merely a few per

Conceptual Basis for MS-based assay developments

cent. The data situation is similar for determining vitamin D with the LC-MS/MS in comparison to the immunoassay. The practical side in the Wisplinghoff lab and in our own shows that the LC/MS can be used well for large series, such as vitamin D and steroids. It has great potential for improving analytical quality compared to the commercial ligand assay.

LC-MS/MS use permits specific detection of myeloma proteins

In the context of therapy control for multiple myeloma, the use of LC-MS/MS permits specific detection of myeloma proteins with a 2000-times higher sensitivity than the immune fixation electrophoresis currently used. That means bone marrow follow-up could become superfluous and earlier recognition of minimal residual disease, respectively a relapse, would be possible.

Assays for tumour markers are known as difficult to compare with each other. Hence the evidence obtained from this parameter is only of limited utility. Potentially there

are new aspects resulting from more specific determination of these antigens using LC-Tandem-MS.

The work of the last decade has proved that mass spectrometric methods are not only qualitatively better compared to ligand assays but also can become routine. Nevertheless, these new methods have not entered daily work everywhere. Even in the context of research studies inferior methods are often still used.

Reasons for this could be that test development plays almost no role in the professional training for laboratory medicine. Frequently the medical side also lacks the methodological understanding. However the questions arise in laboratory medicine.

It is the specialists' responsibility in laboratory medicine to assure that analysis remains up to date. This expertise can only come from him since the exclusively clinical physician can only roughly estimate the influence of the methods used on the diagnostic process and scientists working only methodologically lack medical expertise.

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Early fungal detection eases treatment decisions

The broader development of in-house procedures and the related expertise also makes it possible to develop scientific questions in the out-patient area, a field currently completely neglected, but which also affects a large part of the general population.

Economics: the manufacturer's income aspects are drivers

Practical aspects such as employee qualification and technical skills for operating the machines are evaluated differently. Our experience is that reliable routine use of LC-MS is possible after appropriate initial training. The necessary knowledge for methodological development grows naturally and constitutes a laboratory's valuable capital.

With commercial fully automated systems it is important to recognise that here the manufacturer's income aspects are drivers. Parameters are offered from which the manufacturer expects the greatest profit by virtue of high throughput and not necessarily those that are the most sensible medically. Naturally, commercial fully-integrated systems will always be more expensive than the corresponding in-house procedures.

This places the laboratory in the (contradictory) situation that the income for the high volume and hence cost-effective parameters flows to the manufacturer, while the more expensive special parameters must also be performed at greater expense with an in-house method with a low number of samples. However, the general use of in-house tests results in a reasonable mixed calculation with synergies and broader utilisation of available expertise. This factor appears especially important given current economic pressure with everyone's earnings expectations.

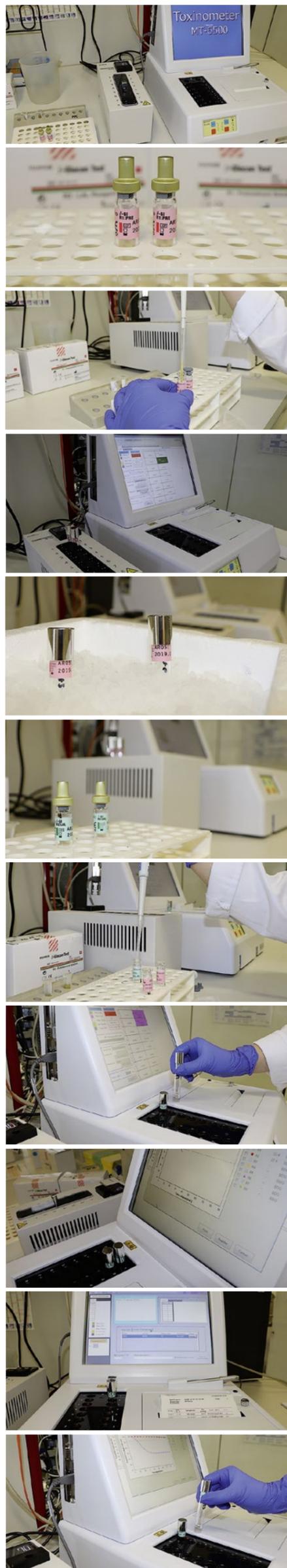
As a rule, although the investment costs for LC-MS/MS are substantial, subsequent costs for test development and operation are low. €700 for a HPLC column may seem an expensive acquisition, but with a service life of 20,000 injections yields a price of 0.035 euros per measurement. Naturally, the establishment of expertise is also not free, yet it is a sustainable investment. In today's competitive situation this gives the lab the opportunity to react flexibly to changing demands and still offer the highest level of analysis.

Still viewed as an expensive niche method for highly specialised analysis

The application of LC-MS/MS in clinical routines is still viewed as an expensive niche method for highly specialised analysis. This perception is obsolete since there are many robust and reliable options available to use.

It is desirable for laboratory medicine, as a specialty, to focus more on the knowledge in methodological development, also for more demanding procedures, such as mass spectrometry, currently performed so often by chemists. The methodological work would open many more diagnostic options in the clinical context than are currently practised.

Funding entities must recognise that qualitatively high-value analysis constitutes a less expensive alternative to merely cheap test methods. This can gain importance when medico-legal implications are considered.



At the National Reference Centre for Invasive Fungal Infections (Hans-Knöll Institute Jena) and the Institute for Hygiene and Microbiology, Würzburg University, Professor Dr. Oliver Kurzai and his team utilise the fast and user-friendly β -D-Glucan Test supplied by FUJIFILM Wako Chemicals Europe GmbH to check immunocompromised patients for signs of life-threatening, invasive fungal infections.

Invasive fungal infections represent a significant health risk for immunocompromised patients. Beta-D-glucan is a marker which facilitates the early detection of these life-threatening fungal infections. The β -D-Glucan Test, developed by the diagnostics department at FUJIFILM Wako, is aimed at also achieving fast (1→3) β -D-Glucan Test results for individual patient samples. β -Glucan is a component of the fungal cell wall which circulates in the affected patients' blood. The detection of β -Glucan therefore helps to diagnose fungal infections. The system has been available as a certified assay for measuring (1→3) β -D-Glucan in the serum or plasma since 30th October 2018 when the CE-mark was awarded. It is based on the LAL (limulus amoebocyte lysate) cascade reactions which can be measured in hospitals with a kinetic turbidimetric monostest procedure.

During a year-long test phase carried out in cooperation with the University Hospital Würzburg, Professor Kurzai has been using the β -Glucan to monitor patients at risk of fungal infections caused by candida species, but also to detect infections caused by other species of fungi. "The test also enables us to measure fungal infections in individual samples, relatively independent of the pathogens. With individual samples we can also determine very quickly if a patient is possibly suffering from a fungal infection or not," says Kurzai.

Blood sampling instead of invasive intervention

The test is particularly relevant for patients in intensive care. "Serious, invasive fungal infections are not that much of a problem in outpatient care," says Kurzai. Patients with life-threatening illnesses such as severe neutropenia, or immunosuppressed patients who are developing pneumonia (such as HIV-positive patients) are at higher risk of infection. The procedure can also be used for the detection of pneumocystis pneumonia in AIDS patients. "This test has considerable advantages for these patients as it can be carried out without invasive diagnostic procedures – a simple blood sample suffices for the β -Glucan Test," says Kurzai. Haematological patients at risk of invasive fungal infection of the lungs are tested for Galactomannan and β -Glucan, with Galactomannan being a specific marker for aspergillosis. Kurzai summarises: "With many infections, be it sepsis caused by candida or pneumonia caused by pneumocystis, we know that the outcome worsens dramatically when the infection is not treated early enough. Scientific literature confirms that the window of opportunity where the right treatment must be given is just a few hours long."

Fast and precise diagnosis

"With the new system, we usually receive the test result on the same day within just a few hours – a



Oliver Kurzai is head of the Institute for Hygiene and Microbiology at the University of Würzburg, as well as head of the Leibniz Institute for Natural Product Research and Infection Biology - Hans Knöll Institute in Jena, where the National Reference Center is located under his leadership. From 2009 to 2016 he was Professor for Fungal Septomics, Friedrich Schiller University Jena. His research interests include infection biology and immunobiology of human-pathogenic fungi and infection biology and immunobiology of *Neisseria meningitidis*.

big advantage for patients and for us: "The test helps us to decide on the right treatment quickly."

Handling of the test is also very user-friendly, without long "hands-on time." "Feedback from our laboratory is decidedly positive," confirms Kurzai. "Training a medical laboratory technician can easily be carried out in a week, or at a push in just two days."

Up to now, the Institute for Hygiene in Würzburg had no procedure available for the detection of the β -Glucan parameters. "This is why we used other diagnostic tests to rule out fungal infections, such as the detection of antibodies or of certain antigens. These methods usually take longer, and studies show that the sensitivity and specificity is not as good as that of the β -Glucan Test. "Some of these procedures, which are still widely used, are so bad that they are not even recommended in the guidelines," says Kurzai.

Advantages and disadvantages

The detection of β -Glucan can be used as a screening test for fungal infections – many pathogenic fungi can lead to a positive test. "This can also be a disadvantage," says Kurzai. "If the test is positive, there is no certainty which type of fungal infection the patient is suffering from. Also, some types of fungi do not lead to raised levels of β -Glucan. A further disadvantage is that β -Glucan is found in numerous materials and infusion solutions, which means there is a certain risk that the test generates a false positive result."

Kurzai will continue to systematically collate the parameters and data for the β -Glucan Test at his Institute until the end of the year. The first results are expected to be published at the beginning of 2019. "Our results so far don't yet show how high the number of false positive results is for the procedure, which is something to keep in mind when interpreting the test results." However, Kurzai is sure about one thing: "The preliminary evaluation of our data indicates that the β -Glucan Test is an important, additional option to improve the management of severely ill patients and risk patients."



The ready-to-use reagents of the β -Glucan Test simplify the handling and procedure of testing: After pretreating samples at 70° C in the thermostatisation and subsequent cooling on ice, aliquots are transferred into the LAL reagent and mixed. The Toxinometer MT-6500 measures turbidity and calculate the results quickly and reliably within a short time.

Aiming for 45 linked laboratory structures

New Dutch digital pathology advances

IT efforts have been made to digitise pathology in the Netherlands, where the Dutch pathology network PALGA has run since 1990, connecting all of the Netherlands' laboratories.

Paul J van Diest, head of the pathology department at the Utrecht University Medical Centre, presented the brand new Dutch digital pathology platform during ECP 2018. Launched this year, this enables quicker, easier consultation. 'We currently have 14 labs with decent digital pathology infrastructure,' he explained. 'Many are working to become digital, and in the next five years we will probably have 45 different structures offering digital pathology.'

Presently two labs are working completely digitally, three labs work partly digitally for diagnostics, two labs are dedicated to subspecialisation, and seven more academic labs, equipped with scans for research and teaching purposes, want to go digital very soon.

Pathology has myriad applications. Patients can be referred for a consultation or within research, and also for pathology material revision and quality control – not just image control quality, but also to reformulate results in local and up-to-date jargon. The purpose of referral can also be to compare new material or material for demonstration at multidisciplinary meetings, and further testing.

Per year, Dutch pathology services deal with, on average, 27,000 cases, including 10,000 for second opinion alone. Turnaround of findings can be up to 14 days, with 15% of the cases taking over four days, a time van Diest and team have tried to reduce as much as possible. They concluded that nothing works as fast as a digital solution.

'During this time the patient has to wait for definite results and treatment, which seriously impairs quality of life and involves a lot of stress,' he pointed out. 'There's also a loss of productivity, because, in this window, people are usually not working. We've done some projects to reduce that period to two days.

It's good, but digitally it comes on the same day.'

A digital solution is much easier and uses efficient data. Scans and slides are placed directly on the server and a click sends them to another lab, he added. 'These benefits prove useful in complicated cases; they save time and travel.'

The PIE project

The increasing need for lab-to-lab communication triggered the creation of a national solution, to avoid risk of incompatibility with locally developed tools.

A few years ago, van Diest and other researchers began the PIE project, a national platform for safe exchange of digital images and pharmacy labs. Using this tool provides many benefits, he said, including rapid and low-cost consultation, use in provisions and panels, and improved results for patients.

The Netherlands had a big asset when setting up the platform, with the PALGA network. 'All labs are already connected to a central archive. We have a good and unique infrastructure.'

The platform went live this year, supported by the Dutch society of pathology, the Netherlands Comprehensive Cancer Centre, the company Sectra, Deutsche Telekom and RAM-IT.

The system

Images are uploaded to the central server; a message goes through PALGA, which ensures a separation between patient data and images to guarantee data anonymity and safety. A message is then sent to another lab; those pathologists log into the system, view the images, their opinion is returned via PALGA.

'There is no need to e-mail or fax; it's all within the system,' van Diest explained. 'For panels, it works the same way just with more pathologists involved.'

He has a lot of experience with tenders and recommends first checking whether the system is fast enough and vendor independent. 'It needs to be fast otherwise we get bored and stick to the sides. We

Other important issues to consider when selecting a digital pathology platform are security, uptime – over 99% – and connectivity with other key tools like PALGA, and different Lab Management Systems (LMS) in the Netherlands.

Storage is essential. For now, the PIE team keeps images for at least three months, leaving plenty of storage space available, but they will expand this soon.

PIE in the first weeks

Security issues are solved and validation is ongoing, according to Van Diest. A pilot consultation was run between UMCU and Radboud UMC Nijmegen during two weeks in the summer. Forty-five fairly difficult cases of lymphoreticular diseases, with 10 to 15 slides per case, were automatically uploaded. Results were very encouraging.

'We got the answer for most cases on the same day. Some cases took two days to be solved; they just had to be revised for multidisciplinary (MS) meetings.

In none of the cases was the need expressed to send over physical slides.

In the framework of quality control for MS meetings, there were no discordances with gold standard by microscope check. That result shows the potential power of the system,' he noted.

Next, all Dutch labs must be connected; presently only six are, but many are interested. 'They still need a scanner,' he said. 'So, it will take time, but we organise roadshows to explain to them how to connect to PIE.'

The platform has neither sound nor video yet, but these will come



At VU University medical centre (VUMC) in Amsterdam, Paul J van Diest gained his PhD in medicine followed by Board certification in Pathology in 1996 and his role as Consultant Pathologist at VUMC's Pathology Department. In 1999 he became Associate Professor and, in 2001, full Professor. In 2003 he moved to head the Pathology Department at the University Medical Centre (UMCU) in Utrecht. 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, Italy. He is on the editorial board of 23 international journals, has published around 700 papers in peer-reviewed journals, and personally supervised about 70 PhD theses. He has also been active as secretary and president of various international societies.

soon, as will integrated image analysis and deep learning algorithms within a couple of years, he estimates. Mobile device functionality is already available, so any pathologist can communicate with his/her iPad with a pathologists' panel.

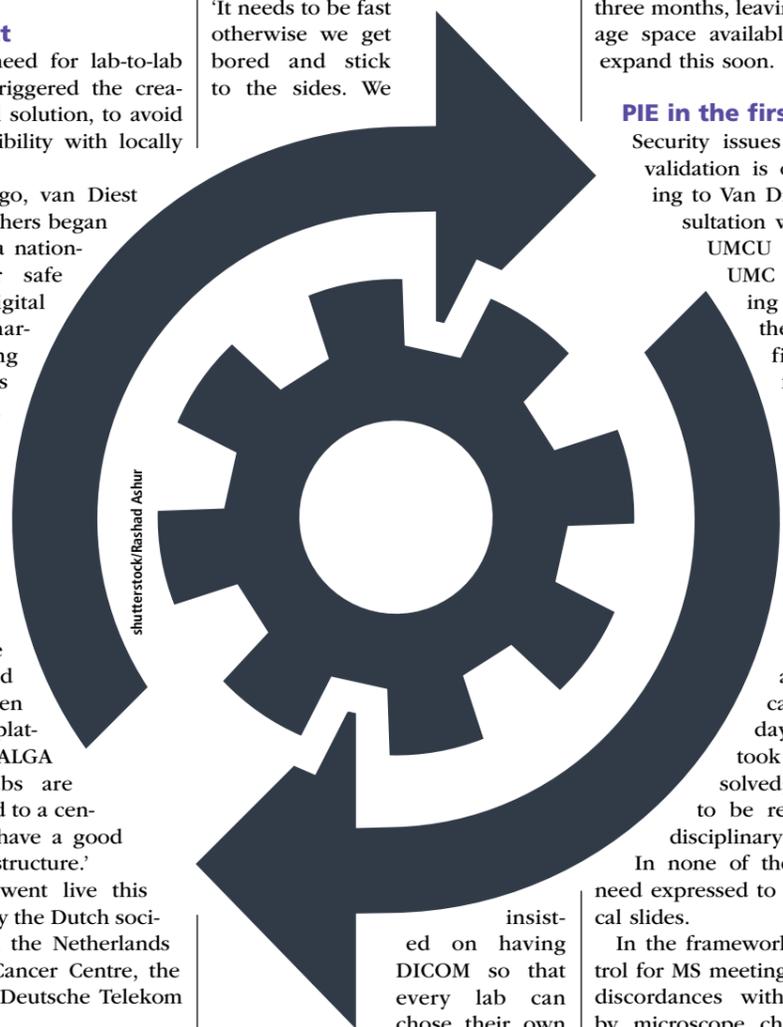
In future the service could upscale to the Dutch speaking area of Belgium and, in English, to the rest of Europe and the USA, he suggested.

Cooperating through PIE could be a stepping-stone for central storage, he added. 'All the labs are struggling with expensive central storage for images.

'We keep all our images with 1PB of digital images going seven years back; it's considerable information – an expensive hobby. Why couldn't we do all this together?'

Research for clinical trials and teaching – e.g. all those with sets of images of complicated cases could share them – could also be done easily through PIE.

Annual running costs for PIE range between 8,000 and 15,000 Euros, through a subscription paid by the lab. CCC Netherlands and PALGA co-finance the costs, but, van Diest said, 'You must think about what you save in your lab with such an investment: administration costs, reduction of waiting times for results and treatments, etc. People ought to find this worth it.' MR



Pathology is the only path

Moving us towards precision medicine

The European Society of Pathology (ESP) holds its European Congress of Pathology (ECP) at different venues annually. This year, in Spain, 3,448 delegates from 87 countries attended. There, ESP president Dina Tiniakos spoke with Mélisande Rouger about the increasing role of pathology in precision medicine including challenges linked to digitisation.

'Precision medicine is the centre-point for cancer management, but also important for non-neoplastic diseases,' Tiniakos explained. 'Oncologists need the correct histological diagnosis and information on underlying gene mutations to offer the right personalised medication. Pathologists play a key role in this respect, because they make the diagnosis and also offer information about the mutations present in a tumour.'

'Pathologists make the conventional diagnosis using glass slides and diagnose the presence and expression of certain proteins using immunohistochemistry. We also perform molecular pathology testing on tissue samples taken from the tumour, and can give a combined report in addition to the traditional histology used several years ago.'

'For breast cancer, for example, pathologists can give information about oestrogen and progesterone receptors status and HER2 protein expression status. Patients whose tumour has over-expressed HER2 protein due to underlying gene amplification can be treated with anti-HER2 monoclonal antibodies. Pathologists have a nodal role in guiding patient management. Therefore, the only path to precision medicine is through pathology.'

Digital benefits

'With digital slides, we can work directly on our computer screen and slides are digitally stored. Collaboration and consultation are easier – slides can be shared from anywhere. When I'm in Athens, I can assess the slides I stored at Newcastle University, for example.'

'Digital pathology is still not being used routinely in most labs, but it's the future – where we are going. We need to ensure all remaining issues are properly tackled.'

'A major drawback: a large digital storage space is needed. Digital slides are huge. Labs that want to go digital need to apply to clouds and rethink their information technology (IT) strategy, to find appropriate solutions.'

'Pathologists don't work as fast as they'd like, because it takes more time to interpret digital slides than glass slides. I still prefer to look at glass. Digital evaluation requires a long learning curve, and time to change the way our brain works looking at slides.'

'Young pathologists have an easier time because their brain is more adapted to working with the screen. It will become easier for everyone else as well. Studies show there are no significant differences between



glass and digital slides. Most importantly, the pathologist needs to be well trained to interpret both glass and digital histological slides.

'The FDA doesn't approve of histological assessment with digital slides in a clinical trial setting yet. There isn't enough evidence regarding the agreement on histological scoring between glass and digital slides.'

IT solutions in clinical practice

'We use tools that help us objectively to evaluate immunohistochemical stains for scoring, for example presence of oestrogen and progesterone receptors in breast carcinoma, or Ki67 proliferation index in neuroendocrine tumours. Dedicated software can measure cell numbers with

nuclear immuno-sustaining indicating the presence of receptor expression or cell proliferation, instead of manually counting cells. In Athens we use a commercially available system, but it's also possible to develop a simple "home-made" solution, with local IT colleagues.'

'IT tools are good companions in our traditional pathology diagnosis; they can save time.'

'AI is a very interesting development for pathologists. Machine learning may help routine diagnosis using algorithms that can pinpoint areas of interest in a section, or classify simple benign cases as such, for example.'

'These tools may help us decide if a certain feature is present or not. In liver pathology, it's still experimen-

tal, but there are platforms that can identify the extent of steatosis, i.e. fat in liver.'

'Pathologists have to train the machine – a lot of work, but this will become a great tool. It's only the beginning and something pathologists should look positively upon.'

'A number of issues remain to be tackled, including using patient data to train the machine, even if data is anonymised. The controversy surrounding the deal between an AI start-up and the Memorial Sloan Kettering Cancer Center recently showed the delicacy of this issue (26/9/8:- www.healthimaging.com)'

Challenges

'We need to be well trained to use these tools properly. The ESP has



Dina Tiniakos, President of the European Society of Pathology (2017-19), is Associate Professor at the Medical School in the National & Kapodistrian University of Athens, Greece, and Senior Lecturer at the Institute of Cellular Medicine, at Newcastle University, UK. A specialist in hepatobiliary pathology, she researches fatty liver disease and hepatocarcinogenesis. She is also the author or co-author of around 130 peer-reviewed scientific articles and chapters in liver pathology and histology, and is on Editorial Boards of several scientific journals and is an external assessor for various European research grants bodies.

an IT technology working group, which organises congress sessions. There was a dedicated symposium on this at the ECP. No special guidance is issued but training pathologists in effectively using IT is among our aims. The ESP educational portal enables members to access all educational material recently collected throughout our courses. 'ESP courses are run by experts for residents and consultant pathologists across Europe. For young pathologists the ESP funds specialised 1-3-month training in centres of excellence, with all expenses covered (Giordano Fellowship).

At the ECP 2018 free access and over 150 grants were awarded, with travel and accommodation funding for young pathologists who submitted an abstract accepted for presentation at the congress. In five years, about €200,000 grants and fellowships were awarded. MR

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