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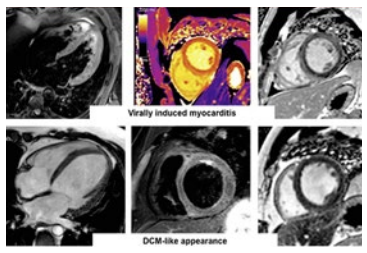
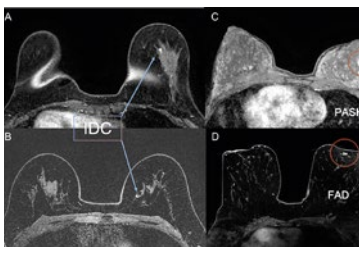




AMR research gains $1 billion funding

A unique, ground-breaking global campaign, which has seen major pharmaceutical companies unite to fight antibiotic resistant infections, has been launched with a one-billion-dollar investment fund, Mark Nicholls reports.

The Antimicrobial Resistance (AMR) Action Fund – unveiled in Berlin and Washington in July – with a further launch in Tokyo, aims to help save the collapsing antibiotic pipeline and make 2-4 new antibiotics available within a decade. More than 20 biopharmaceutical companies have joined with philanthropies, development banks, and multilateral organisations to strengthen and accelerate antibiotic development to address the rapid rise of antibiotic-resistant infections (i.e. antimicrobial resistance).

The ongoing Covid-19 crisis has so far killed more than 500,000 people worldwide, yet AMR is believed to kill 700,000 annually. There are fears that deaths could reach 10 million a year by 2050.

The AMR Action Fund, an initiative of the international body representing the R&D pharmaceutical industry, the IFPMA (International Federation of Pharmaceutical Manufacturers & Associations), will provide financial resources and technical support to help biotech companies bring novel antibiotics to patients. Nearly US$1 billion has already been raised to support clinical research.

Currently, there is no viable market for new antibiotics and thus, in recent years, a number of antibiotic-focused biotechs have left this field. There are few novel antibiotics in the pipeline.

The AMR Action Fund intends to invest in smaller biotech companies focused on developing innovative antibacterial treatments; provide technical support to portfolio companies, giving them access to the expertise and resources of large biopharmaceutical companies, to strengthen antibiotic development, and support access and appropriate use of antibiotics; and bring together a broad alliance of industry and non-industry stakeholders.

The concept of the AMR Action Fund was developed by the IFPMA and the Biopharmaceutical CEOs Roundtable (BCR), and biopharmaceutical companies and foundation, in collaboration with the World Health Organisation (WHO), The European Investment Bank (EIB), and the Wellcome Trust.

The Fund is supported by biopharmaceutical companies and foundations such as Almirall, Amgen, Bayer, Boehringer Ingelheim, Chugai, Daiichi- Sankyo, Eisai, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, LEO Pharma, Lundbeck, Menarini, Merck, MSD, Novartis, Novo Nordisk, Novo Nordisk Foundation, Pfizer, Roche, Shionogi, Takeda, Teva, and UCB.

Joining the launch were several CEOs from those companies, along with Dame Sally Davies, UK Special Envoy on AMR; Dr Tedros Adhanom Ghebreyesus, Director General of the WHO; Werner Hoyer, President European Investment Bank; Jeremy Farrar, Director Wellcome Trust; and Stella Kyriakides, European Commissioner for Health and Food Safety. Government ministers included Jens Spahn, Federal Minister of Health, Germany; Magnus Heunicke, Minister of Health and Senior Citizens, Denmark; and Agnès Pannier-Runacher, Secretary of State for Economy and Finance, France.

'The spread of drug resistant infections can no longer be effectively treated by existing antibiotics,' stressed Farrar, as Ghebreyesus described AMR as a 'slow tsunami that threatens to undo a century of medical progress'.

Describing AMR as a global challenge, Spahn drew attention to the German Antibiotics Resistance Strategy 2020, which aims to make decisive advances in research and development in the field.

'AMR is not only predictable, but also preventable,' Kyriakides added. With the aim to make the EU a best practice region and a global leader on tackling AMR, she said: 'Tackling AMR is everyone's responsibility and should be everyone's priority. No state, no region, can do this alone; what we need now is global action.'

Other key speakers included Hubertus von Baumbach, Chairman of the Board of Managing Directors, Boehringer Ingelheim; Stefan Oelrich, CEO Bayer Pharmaceuticals; and Stefan Oschmann, Chairman of the Executive Board and CEO of Merck.

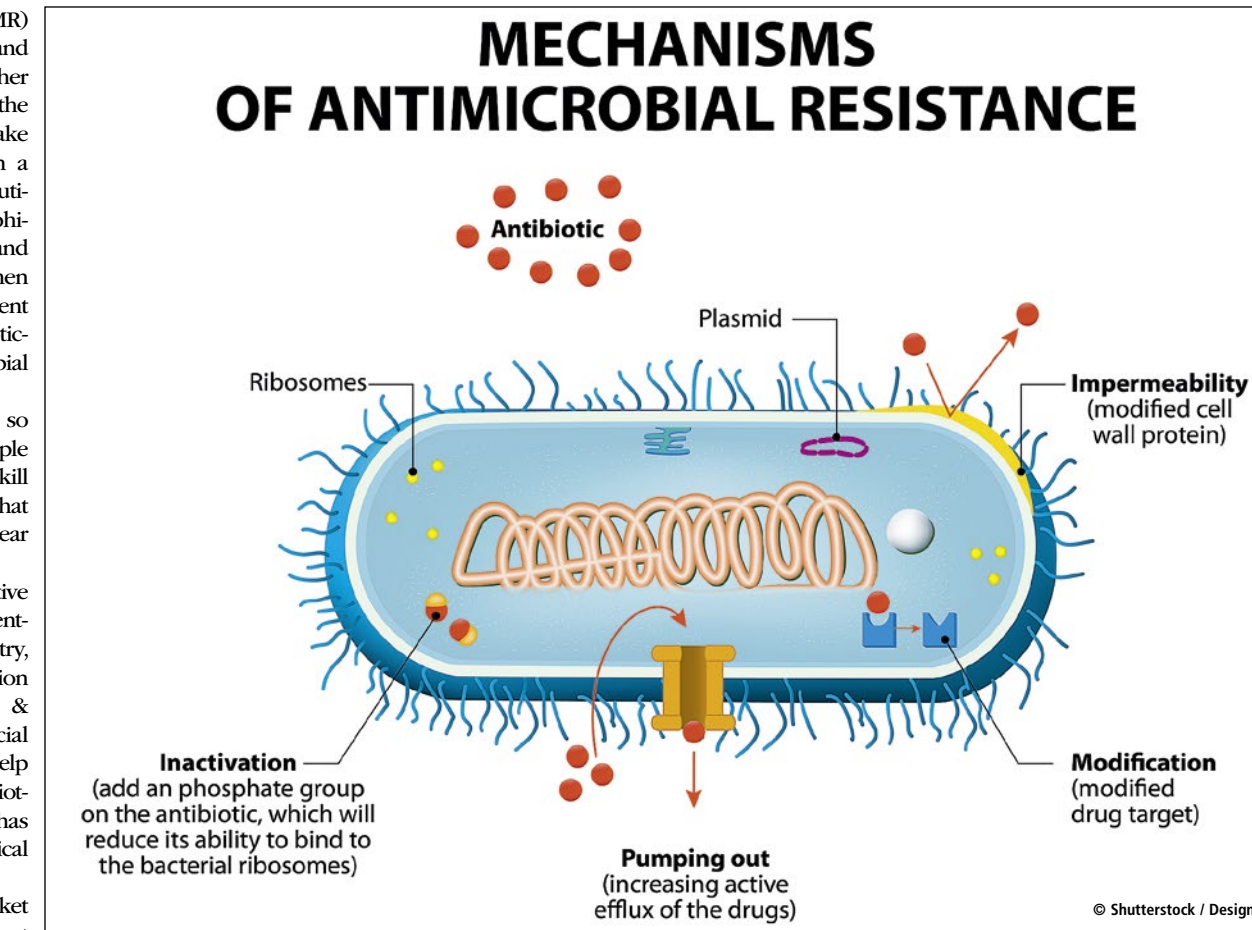
Boehringer Ingelheim does not currently conduct antibiotic research, said Baumbach, but his company has invested because it recognises the huge scale of the problem.

IFPMA Director-General, Thomas Cueni, said that while Covid-19 had dominated the last few months, not so much has been heard of AMR in recent years.

'Unlike Covid-19, AMR is a predictable and preventable crisis,' Oelrich stated. 'We must act together to rebuild the pipeline and ensure that the most promising and innovative antibiotics make it from the lab to patients.'

With no new class of antibiotics since the late 1980s, and the over-use of antibiotics for humans and animals, and the exit from relevant treatments by big pharma companies he warned that the pipeline for new antibiotics looks 'pretty grim'.

This is a science as well as economic problem, he pointed out. 'Now there is no viable economic system for development for new antibiotics, the economic model is broken and with a broken economic model the right kind of research and development in antibiotics has not taken place', he explained, but he sees that industry has now 'stepped up' in collaboration with the WHO, EIB and Wellcome Trust to create the $1 billion fund. 'The focus of the investment will be on start-up and biotech companies, which see it as a lifeline as there is no money available to fund clinical research. This is a bridging solution. The AMR Action Fund aims to provide the bridge, and bring 2-4 new antibiotics to the market by 2030. That is a significant historic milestone, with industry stepping up and responding.'



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Dr Tedros Adhanom Ghebreyesus, Director General, World Health Organisation

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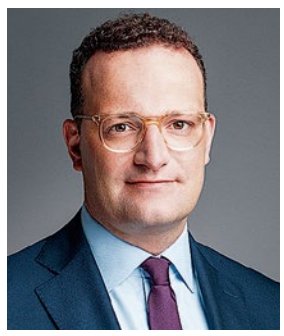
Dame Sally Davies, UK Special Envoy on antimicrobial resistance (AMR)



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Jens Spahn, Federal Minister of Health, Germany

www.healthcare-in-europe.com

Largest UK nitrogen dioxide levels: London and Midlands

Air pollution linked to higher Covid-19 mortality

Scientists have unearthed a possible link between the severity of Covid-19 and air quality. The preliminary study - looking at whether areas with higher levels of air pollutants in England are associated with a larger number of cases/deaths from Covid-19 – was conducted by a team from the University of Cambridge.

Report: Mark Nicholls

Aware of the effects that air pollutants have on human health – and that initial symptoms of Covid-19 include fever, with some patients developing serious respiratory problems – for their study, the scientific team used publicly available data from multiple air monitoring stations across the country where a minimum of 2,000 SARS-CoV-2 infections and 200 deaths were reported in the period from February to early April 2020.

They analysed the data on total Covid-19 cases and deaths, against the levels of three major air pollutants, collected between 2018 and 2019, when no Covid-19 case was reported.

People exposed to higher levels of certain pollutants were found to be at higher risk of Covid-19 infection and/or death when taking into account differences in population density from region to region.

'We used different approaches to reach these conclusions,' researcher Marco Travaglio explained. 'After gathering air pollution data from the European Environmental Agency, we then compared it to lab-confirmed numbers of cases and deaths from Covid-19 as reported by government official sources.

'We used multiple statistical models to account for the effects of demographics and found that air pollution is strongly associated with Covid-19 mortality, whether you live in a highly populated area or not.'

The largest number of Covid-19 deaths in England occurred across London and the Midlands, reflecting the geographical distribution of Covid-19 related cases. Previous studies have shown that the annual average of nitrogen dioxide concentrations are largest in these two regions.

'Our results provide the first evidence that SARS-CoV-2 case fatality is associated with increased nitrogen oxide and nitrogen dioxide levels in England.' London, the Midlands and the North West show the largest concentration of these air pollutants, with Southern regions displaying the lowest levels in the country, and the number of Covid-19 deaths follows a similar trend,' explained Travaglio, a PhD student at the Medical Research Counxil (MRC) Toxicology Unit, Cambridge.

While the implications could be far-reaching, the researchers emphasise that their findings are only preliminary and only show a correlation, and that further research is needed to confirm that air pollution makes Covid-19 worse.

'Data is compelling and certainly flags up several important issues,' he pointed out, 'but more work needs to be done before our findings can turn into concrete policies that can aid against the fight against Covid-19.

'The major implication for the time being is that our study raised interesting hypotheses regarding the effect of air pollution on the current epidemic and adds yet another piece to the puzzle and shows that air pollution could be linked to human health in ways that no-one imagined before.' Supported by the Medical Research Council, the research has been carried out by the lab of Dr Miguel Martins at the MRC Toxicology Unit in Cambridge, with Travaglio sharing first authorship of the manuscript with Yizhou Yu.

It also includes evidence from Northern Italy and the USA that high levels of air pollution are linked to deadlier cases of Covid-19.

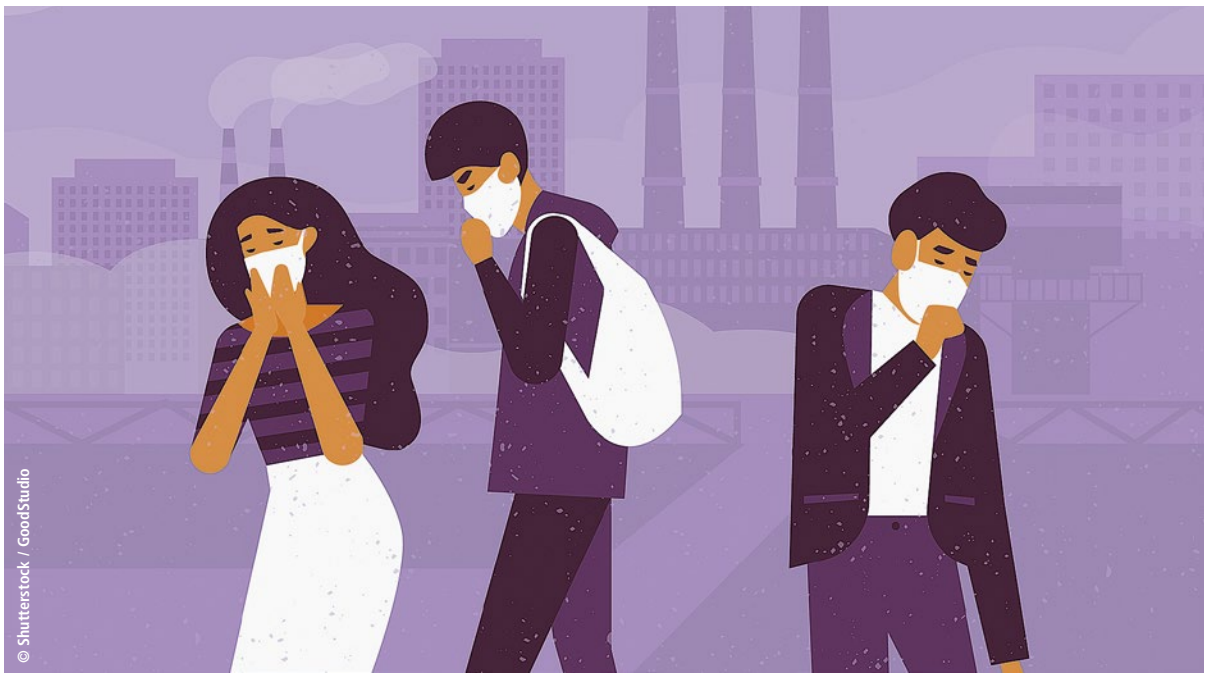
This comes at the height of the UK coronavirus lockdown with significant falls in car and public transport use.

In addition, Department for Energy, Food and Rural Affairs (Defra) monitoring data for nitrogen dioxide (NO2) in London, Leeds, Manchester, Cardiff, Edinburgh, Liverpool, Bristol and Newcastle, found big reductions in emissions (at the end of March 2020) compared with the same time last year.

Despite the fall in NO2 emissions, citizens in UK cities were warned by the European Public Health Alliance (EPHA) that exposure to air pollution could increase their risk of dying from Covid-19.

In 2019, ten hospitals in the most polluted areas of London were equipped with air quality monitors to measure levels of toxic air and help protect patients and staff after a study found 60% of hospitals and NHS facilities in inner London were located in areas that exceed air quality pollutant levels.

Marco Travaglio is a second-year PhD student at the University of Cambridge. Prior to the Covid-19 outbreak, his project mainly involved looking at selective cell death in cell models of Parkinson's disease but, more recently, in the light of the coronavirus crisis, he and his team have re-focused efforts towards Covid-19 research.



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From clinician to hospital medical director

'Lead from the front'

Making the transition from clinician to a senior hospital management role can prove challenging. Professor Erika Denton did it – whilst also retaining some clinical responsibilities.

A radiology background, Denton believes, is a major asset in making the move into high-level management. Currently the Medical Director of the Norfolk and Norwich University Hospital (NNUH) in the east of England, she remains a consultant radiologist (with a specific interest in breast imaging), and Professor of Radiology at the University of East Anglia.

Denton describes her transition from clinical to management – with a few pointers from her career that prepared her for the role. She had found herself in the role with very little notice after the publication of a report by UK regulator the Care Quality Commission (CQC) into the hospital's activities. 'Such a role had been in my mind as being a good thing to do, but I had not anticipated it at such short notice,' she explained. With a state school background in the United Kingdom, Denton recalled her days at medical school, which she did not particularly enjoy, but she loved being a junior doctor, even when on medical rotation at Medway Maritime Hospital in Kent. 'It was all a good grounding and I learned to not fear talking to anybody.'

Training scheme and radiology academy

Moving from London to rural Norfolk in 1999, she became director of breast screening at the Norfolk and Norwich Hospital (which would later become the NNUH) and had other management roles at the new 1,200-bed University Hospital which opened in 2001 and employs over more than 8,000 staff to provide care for a million people. There, she campaigned for more junior doctor posts, helping to establish a training scheme followed by a radiology academy.

Denton also had several national roles before taking up her present NNUH position in 2018. 'One thing that struck me about being a leader is that, coming through the imaging world where there is constant change, radiology sets you up really well for leadership and the agile world of medical management.' However, she warned of the need to recognise the importance of a multi-disciplinary approach.

'Remember,' Denton advised her audience, 'you are only one small

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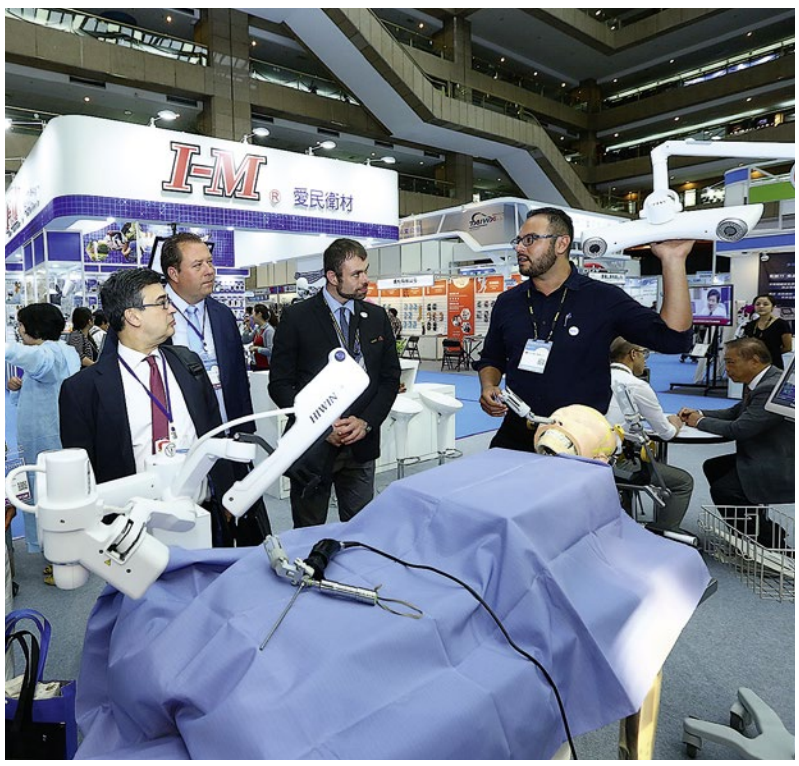
Scheduled: Virtual and physical healthcare exhibitions

Medical Taiwan will take place as planned



Taiwan. 15-17 October – A physical international exhibition and "virtual trade show" hosted by the Taiwan External Trade Development Council (TAITRA) will run as scheduled at Taipei Nangang Exhibition Center.

'With both featuring exhibits at three-dimensional (3-D) booths simultaneously, Medical Taiwan will be a perfect online/offline platform that pulls exhibitors and buyers together and helps usher in business opportunities in the healthcare industry, thereby promoting continuous development of international economy and trade,' the organiser points out.

Using virtual reality (VR) technology, 3-D booths will exhibit 700 medical products from more than 200 medical device manufacturers.

A tour broadcast will transport visitors around international exhibitors

For the physical exhibition, a 'trade show tour' broadcast will transport viewers to some of the latest products and technologies, and see the international healthcare players with no social distancing.

Visitors will be able to explore an entire epidemic-prevention ecosystem, the organiser adds, as well as the latest smart healthcare solutions. 'Taiwan's high-quality epidemic prevention products and the potential of its digital healthcare industry are on full display. One of the highlights – TAITRA's Taiwan Anti-Covid-19 Pavilion – is instrumental in facilitating medical and healthcare information exchanges via video conferencing, matching and allocation of medical materials, sharing of epidemic prevention experiences and updates of medical technology. It shows what Taiwan's healthcare industry can offer to the whole world.'

Online sourcing meetings will connect with buyers

The Taiwan government lists biotech and medical technology industries among the country's six core strategic industries. 'The policy resonates in various government agencies, industry associations and research institutes and many of which, such as Ministry of Health and Welfare, Industrial Development Bureau, Metal Industries Research & Development Centre, Taiwan Medical and Biotech Industry Association, Taipei Medical Instruments Commercial Association, Industrial Technology Research Institute, Taiwan Nonwoven Fabrics Industry Association, Footwear and Recreation Technology Research Institute and Taiwan Sports Technology Association, will bring their members to take part in this year's show, demonstrating the achievements of Taiwan's healthcare industry and its vision for the future,' the organiser continues.

Firms will gain from real-time connections with important buyers

Online sourcing meetings will also enable local companies to connect with important buyers gathered by the 63 overseas offices of TAITRA in real-time, hoping it will lead to further cooperation in the future.

The 'Medical Taiwan Forum' will also be held during the show, focusing on the smart healthcare post-pandemic industrial development.

Details: https://www.medicaltaiwan.com.tw/en/index.html

part of a huge team but, when in a senior management position, you are a very visible component and a big part of leadership is leading from the front.'

Over her career, she has established screening programmes in her hospital catchment area, as well as implemented PACS nationally in the UK, worked with diverse teams on running population-based healthcare systems, new service delivery models, and acted on national and international imaging advisory bodies.

Denton acknowledges that she has 'taken flak' from colleagues along the way but remains a firm believer in teamwork. With UK hospitals busier than ever, particularly with winter pressures, she said: 'We have to use our powers of influence as leaders to make the service as safe as it can be.'

Describing the roles within the medical director's job as 'quite a scary list' with high expectations, it covers areas of safety, quality, risk, leading doctors, working with other senior managers and the hospital board, as well as liaising with regulatory bodies.

She spoke about having self-confidence when chairing committees, making good use of time, and juggling work with home life and motherhood, but concluded: 'My biggest tip is be kind to yourself; you need "me" time and perfection is not necessary.' (MN)

Professor Erika Denton is the Medical Director of the Norfolk and Norwich University Hospital Trust, as well as a consultant radiologist and Professor of Radiology at the University of East Anglia. Previously, as the National Clinical Director for Diagnostics at NHS England, and National Clinical Director for Imaging at the Department of Health, her work has included cancer, paediatric, interventional, cardiac and forensic imaging. Her research interests include medical management, interventional procedures in the breast, and breast screening.

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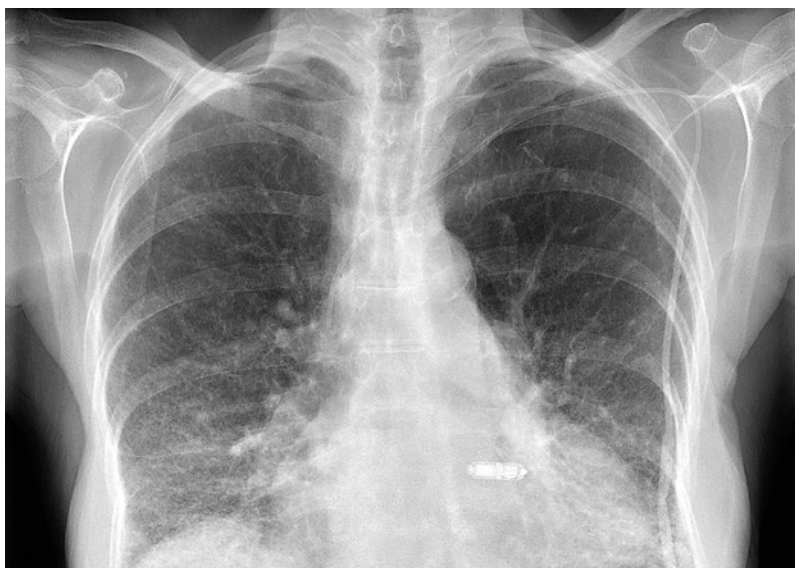
Device to benefit more cardiac patients

The pioneering mini-pacemaker

Belgium - A pioneering new generation of wireless mini-pacemaker is set to benefit many more patients than before.

Following a successful first-in-Europe implantation procedure at the University Hospitals of Leuven, the advance has been described as 'the beginning of a new paradigm of cardiac pacing' with the development of the next-generation mini-pacemaker regarded as a major step forward in this field. Cardiologist and electrophysiologist Dr Christophe Garweg, from the cardiovascular department at the University Hospitals of Leuven, outlined the work involved since 2015 in designing and implanting the first generation of the Micra VR device, which allows asynchronous ventricular pacing (VVI pacing mode).

The second-generation pacing device



Thorax with implanted Micra AV

However, until now, its use has been limited to atrial fibrillation (AF) patients, or those with contra-indication for double chamber pacemaker, which is approximately 16% of current pacing indications.

Now, the second-generation model, the Micra AV, has been developed to allow atrio-ventricular synchronous pacing (VDD pacing mode).

40% of patients can use it

With the new evolution of the Micra pacemaker able to measure cardiac activity in the atrium and, as such, coordinate the electrical activity between atrium and ventricle, it widens the use of the mini-pacemaker to 40% of patients, up from the 16% the first generation for whom it was relevant. Garweg, who also leads his institution's leadless pacing clinical and research program, said: 'The first generation of the device that allows VVI pacing has similar features to a "conventional" ventricular pacemaker including accelerometer driven rate responsive pacing, automated pacing capture management. But it only measured the heart activity in one ventricle, so patients who needed to have the heart activity in the atrium measured as well, did not qualify.

'With this new type of pacemaker, we can also treat patients with a complete interruption of the heart activity between the ventricle and the atrium.' The device utilises the new MARVEL (Micra Atrial TRacking Using a Ventricular AccELerometer) custom software developed to detect atrial contraction using the 3-axis accelerometer (AAC) of the Micra, enabling AV atrio-ventricular (AV) synchronous pacing.

Manufactured by Medtronic, both devices are currently the only leadless pacing devices available for clinical use and weigh a mere 2g, with a length of 25.9 mm, a diameter of 6.7 mm, and 8-13-year battery life. The distal end incorporates the electrode and four retractable nitinol tines to ensure fixation in the myocardium. It has also been associated with a 63% reduction of complications, compared to historical groups of patients with a conventional pacemaker.

Continuing clinical trials

While now commercially released, the Leuven department continues to use the device in the context of clinical trials to further improve the technology. It has also previously participated in the Marvel 1 and 2 prospective multicentre studies to assess the feasibility and the safety of clinical use of the Marvel one and two softwares.

Safety and efficacy need confirmation

Garweg stressed that the safety and efficacy of the new Micra AV still must be confirmed in larger populations with a longer follow-up before being widely used in the clinical setting.

In addition to the first implant in Leuven (May 28), similar implants were carried out on the same day in Linz and Santiago.

Garweg believes longer term patient-benefits of this device are the absence of transvenous lead and subcutaneous pocket reducing the complication rate at long-term follow-up. (MN)

Dr Christophe Garweg is a cardiologist and electrophysiologist with the cardiovascular department at the University Hospitals of Leuven, where he also leads the institution's leadless pacing clinical and research program.

Entering a new age of artificial intelligence

AI predicts blood flow to the heart

Report: Mark Nicholls

UK – Artificial Intelligence (AI) has, for the first time, measured blood flow to the heart to help predict which patients may suffer myocardial infarction or stroke.

A research team at University College London and Barts Health NHS Trust and the National Institutes for Health (NIH) in the USA – are optimistic that AI analysis of perfusion maps will be a reliable, convenient and detailed new biomarker in cardiac patient care.

With myocardial perfusion reflecting the macro- and microvascular coronary circulation, the researchers explored the prognostic significance of stress myocardial blood flow (MBF) and myocardial perfusion reserve (MPR - the ratio of stress to rest MBF) in patients with suspected and known coronary artery disease referred clinically for perfusion assessment.

Image analysis was conducted automatically using a novel AI approach and used to seek the associations of stress MBF and MPR with death and major adverse cardiovascular events, including myocardial infarction, stroke, heart failure, late revascularisation, and death.

A strong and independent predictor

'In patients with known or suspected coronary artery disease,' the study concluded, 'reduced MBF and MPR measured automatically inline using AI quantification of cardiovascular magnetic resonance perfusion mapping provides a strong, independent predictor of adverse cardiovascular outcomes.'

Professor James Moon, who led the multi-centre research team, explained that measuring blood flow to the heart has been used for many years, but non-invasive blood flow assessments, including CMR (Cardiac Magnetic Resonance) imaging, remain difficult to analyse in a manner precise enough to deliver a prognosis or recommend treatment.

During the study, the UCL/Barts/NIH team made CMR 'fully quantitative' in measuring the actual amount of blood flow going to heart muscle, using AI to identify where the muscle is and making the process of working out where the blood pool is easier and quicker.

From routine CMR scans from more than 1,000 patients attending St Bartholomew's Hospital and the Royal Free Hospital the new automated AI technique – devised by Dr Peter Kellman and Dr Hui Xue at NIH – was used to analyse the images, enabling them to precisely and instantly quantify the blood flow to the heart muscle.

By comparing the AI-generated blood flow results with the health outcomes of each patient, the team found that those with reduced blood flow were more likely to have adverse health outcomes.

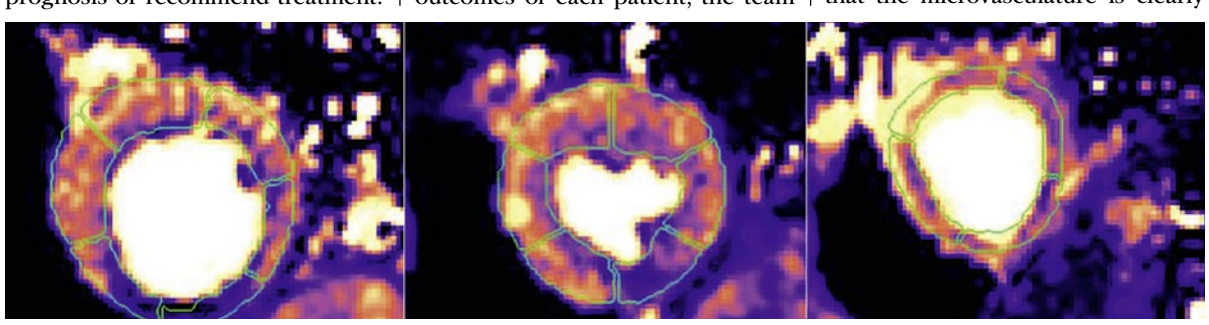
Moon, Professor of Cardiology at UCL and the Clinical Director of Imaging at Barts Heart Centre (BHC), said that AI also could show findings the eye may not have previously seen.

In addition to measuring blood flow to the heart muscle to highlight abnormalities and predict adverse outcomes, AI also identified what may be happening in a wider context with the patient, such as atherosclerosis and age-related stiffening of arteries. 'By just measuring the large arteries, we are missing a chunk of the story about how our hearts are over our lifetimes, and that the microvasculature is clearly changing with age and diabetes and other parameters probably associated with chest pain and outcome. We think those are tractable with a new generation of treatments for the microvasculature disease function,' Moon added.

As a new marker of disease, he acknowledges there is still some way to go to fully understand and realise the potential of this AI advance but also sees an opportunity to develop new therapies for patients with chest pain where the coronary arteries do not appear abnormal.

However, the researchers believe their study has demonstrated the growing potential of AI-assisted imaging technology to improve the detection of heart disease and will have more diverse applications in cardiac care

'It's an indication that we are entering a new era of AI,' said Moon.



Myocardial perfusion maps for a patient with a right coronary artery stenosis. There is hypoperfusion in the basal to mid inferior wall. The perfusion maps have been contoured automatically using artificial intelligence (green) and the myocardial blood flow in each myocardial segment is provided to the operator almost instantly during the scan.

James Moon is a Professor of Cardiology at UCL and the Clinical Director of Imaging at Barts Heart Centre. His research focuses on developing mapping techniques with CMR and measuring diffuse myocardial fibrosis. Having published more than 300 papers, he is also looking at making scans faster and cheaper in improving quality as CMR expands.

Introducing ATEM Mini

The compact television studio that lets you create training videos and live streams!

Blackmagic Design is a leader in video for the medical industry, and now you can create your own streaming videos with ATEM Mini. Simply connect up to 4 HDMI cameras, computers or even technical equipment. Then push the buttons on the panel to switch video sources just like a professional broadcaster! You can even add titles, picture in picture overlays and mix audio! Then live stream to Zoom, Skype or YouTube!

Create Training and Educational Videos

ATEM Mini's includes everything you need. All the buttons are positioned on the front panel so it's very easy to learn. There are 4 HDMI video inputs for connecting cameras and computers, plus a USB output that looks like a webcam so you can connect to Zoom or Skype. ATEM Software Control for Mac and PC is also included, which allows access to more advanced "broadcast" features!

Use Professional Video Effects

ATEM Mini is really a professional broadcast switcher used by television stations. This means it has professional effects such as a DVE for picture in picture effects commonly used for commentating over a computer slide show. There are titles for presenter names, wipe effects for transitioning between sources and a green screen keyer for replacing backgrounds with graphics!

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The ATEM Mini Pro model has a built in hardware streaming engine for live streaming via its ethernet connection. This means you can live stream to YouTube, Facebook and Twitch in much better quality and with perfectly smooth motion. You can even connect a hard disk or flash storage to the USB connection and record your stream for upload later!

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With so many cameras, computers and effects, things can get busy fast! The ATEM Mini Pro model features a "multiview" that lets you see all cameras, titles and program, plus streaming and recording status all on a single TV or monitor. There are even tally indicators to show when a camera is on air! Only ATEM Mini is a true professional television studio in a small compact design!

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Distant experts observe adverse signs

Remote cardiac monitoring

For cardiology patients fitted with an implantable cardiac monitor, cardioverter-defibrillator (ICD) or pacemaker, home monitoring is a blessing. The system also has many advantages for medical staff, as Kristina Rauholt reports. The nurse and Certified Cardiac Device Specialist for Allied Professionals (CCDS) at the Sahlgrenska University Hospital, in Sweden, has worked with home monitoring systems for cardiology patients for many years. She explains how patients and doctors benefit – and how remote monitoring has changed during the Covid-19 pandemic.

Home monitoring systems have been used at the Sahlgrenska University Hospital since 2008. They ensure that the devices work and support patients reliably. 'Every morning we evaluate the report which the system generates automatically when an irregularity is registered,' Rauholt explained. Home monitoring detects changes in heart rhythm, for example ventricular tachycardia or atrial fibrillation. Patients often do not even register these changes, because at first they may not cause any symptoms. 'One of the biggest advantages for us is that the system also alerts us to these "silent problems",' the expert pointed out.

Vice versa, the data can also be utilised when patients report symptoms that indicate heart problems. 'It's an important means of backing up a diagnosis,' she said. This is also the basis for adjusting medication or for synchronising the rhythm more precisely with the help of the implant.

The remote solution saves time, work and cost

The cardiology team evaluates the data sent from the home monitoring system via the mobile network and asks patients to come to the hospital for further investigations if necessary, the expert explained. 'The evaluations also help us to check whether the implant is working correctly – something which patients who have only just undergone surgery tend to worry about. If a patient knows we are continuously monitoring the implant during office hours, this provides a lot of reassurance.'

The home monitoring system raises the alarm if the implant causes problems. 'There are cases where there is a risk that the electrode of an implanted defibrillator will shock the patient, when this is not necessary. This malfunction can become dangerous if it is not detected in time.' GPs are only rarely involved in home monitoring; they may merely use the data generated to confirm a suspected diagnosis, Rauholt said. Accident and emergency doctors, on the other hand, frequently request these evaluations when they need to check whether the ICD has already applied an electric shock.

At Sahlgrenska University Hospital around 800 patients are now connected to the home monitoring system. Cardiologists are only informed about irregularities. 'If all is well with the patient, we don't need any notifications as it would not be possible to cope with the amount of work created,' she added.

Patients benefit from this system as they do not have to go to hospital for as many check-ups. A large number of routine follow-up examinations can be carried out via telemedicine – a significant cost- and labour-saving for the hospital. 'The quality of remote follow-up examinations is equivalent to that of face-to-face examinations – without patients having to make their way to the hospital.'

Particular advantages in times of Covid-19

The latter has become particularly relevant during the Covid-19 pandemic. 'Many patients are anxious and worried about the risk of contracting the virus during a hospital visit.' The standard six-week follow-up examination after surgery has therefore been changed to a tele-examination. Patients are called and asked about their health and whether or not they are experiencing problems with their surgical scars or any other issues 'We used to deem this in-house examination to be very important, Rauholt said. 'However, over the last few months we've had really good experiences with remote follow-up examinations. Patients no longer have to worry about a nosocomial Covid-19 infection, and the tele-examination also causes less time pressure and allows for time more intensively spent with a patient.

Opportunities and challenges

Home monitoring of cardiac patients is an effective tool to considerably reduce strain on patients and hospital staff, Rauholt concludes. 'The system is very reliable. However, the evaluation of the reports requires experience because there is a cer-

The cardiovascular impact of Covid-19

Plus: The multi-organ involvement

The increased Covid-19 risk to cardiac patients was discussed during an online presentation at ECR 2020. Focusing on the prevalence of pulmonary embolism in Covid-19 patients, Dr Karl-Friedrich Kreitner, Professor of Radiology at the Department of Diagnostic and Interventional Radiology at the Johannes-Gutenberg University in Mainz, Germany, discussed hypotheses which can explain cardiac involvement in the course of the disease, and help delegates understand imaging findings of cardiovascular complications.

The 'Non-pulmonary aspects of Covid-19' session, which outlined pathology research on Covid-19, described the many clinical manifestations of the infection and introduced the concept of multi-organ involvement. Alongside Dr Kreitner's presentation on cardiac issues, other contributors will spoke of neurologic manifestations, and the disease in paediatric patients.

The virus affects other organs

When we met, Dr Kreitner stressed that although the virus uses the ACE-2 receptor predominantly located in lung tissue to enter a human, this receptor is also present elsewhere in the body. 'It's also in up to 10% of myocardial cells and in endothelial cells of arteries and veins,' he explained. 'If you are aware of this then you come to the conclusion that the infection is not exclusively localised in the lungs, but can affect other organs as well, including the heart and pulmonary vasculature.'

Among in-patients who die of the disease, Kreitner said there is evidence that not all died due to lung tissue destruction, but there were also other causes, notably pulmonary.

Lab data can help clinicians to assess the risk of Covid-19 patients sustaining thromboembolic disease, he said, in particular checking the D-dimer or fibrin degradation products (FDP) as markedly-elevated D-Dimer and FDP are common in non-survivors of Covid-19.

Recommendations suggest that patients with a D-dimer level below one have a lower risk of thromboembolism than those presenting with a level over one. 'In these newer recommendations there is some risk stratification; that with a D-dimer between one and two you should think of controlling this value and do pulmonary embolism imaging in the further course of the disease. If presenting with values above two, you should immediately test to see whether the patient suffers from pulmonary embolism or not.

'Generally, if values are below one, you can treat these patients with a prophylactic dose of low molecular weight heparin and where the value is above two, you should consider a therapeutic dose of low molecular weight heparin.'

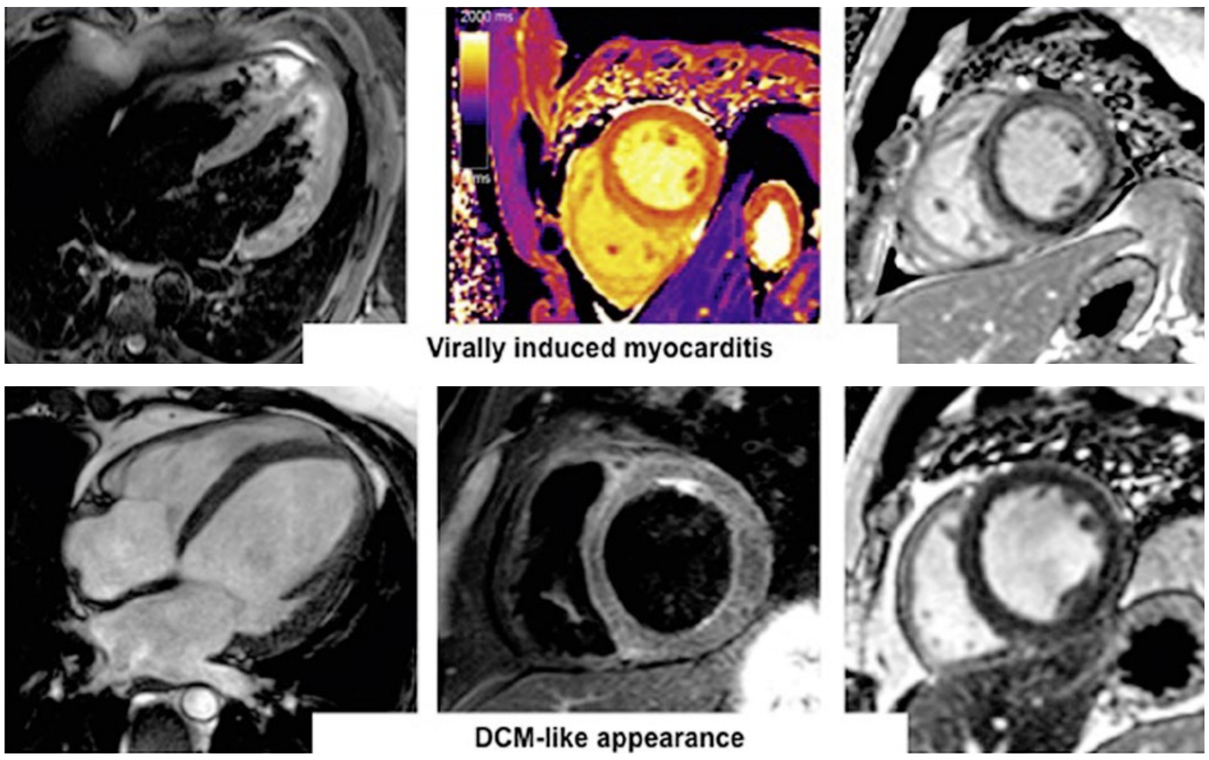
Weighing up risks

The challenge, he pointed out, is to weigh up lowering the risk of thromboembolism against the increased risk of haemorrhage, and it is very important to look at these values when the patient is admitted to hospital.

'With cardiac involvement, Covid-19 patients suffering a cardiovascular disease have a much higher risk of dying from the condition. This is perhaps because their cardiovascular system is not fit enough to face the challenges of this SARS-Cov-2 infection.'

In such cases, clinicians should turn to cardiac biomarkers, especially high-sensitivity troponin and the NT-pro BNP because, when they are elevated, the individual is at a greater risk.

While much of the evidence of this has come from China, Italy and the USA, Dr Kreitner discussed two patients from his department who presented with different forms of Covid-19 myocarditis. 'One presented with a typical viral myocarditis and the second with dilated cardiomyopathy-like appearance with signs of inflammation, so the phenotypes of cardiac involvement have a great diversity.'



Kristina Rauholt-Lundkvist has been a nurse at the Sahlgrenska University Hospital in Sweden since 2006. She is certified as a Cardiac Device Specialist (CCDS) by the European Heart Rhythm Association and the American Heart Society and, as such, manages the monitoring, follow-up and programming of Cardiovascular Implantable Electronic Devices (CIEDs), such as Implantable Cardioverter Defibrillators (ICDs), Cardiac Resynchronisation Therapy (CRT), Pacemakers and Loop Recorders.

tain learning curve involved.' The European Heart Rhythm Association (EHRA) awards the respective certificates which confirm expertise in dealing with these cardiac devices.

This experience can help avoid pitfalls. 'For example, certain drugs make patients experience atrial fibrillation and cause a change in heart rhythm. This is an intentional and desired effect; however, the system perceives it as arrhythmia,' Rauholt pointed out. 'If we know about this effect, we can easily identify the resulting notifications as false alarms and act accordingly.'

At the end of the day, she concluded, home monitoring has reduced many of the obstacles for both medical staff and patients – and has proven a particularly beneficial tool during the Covid-19 pandemic.

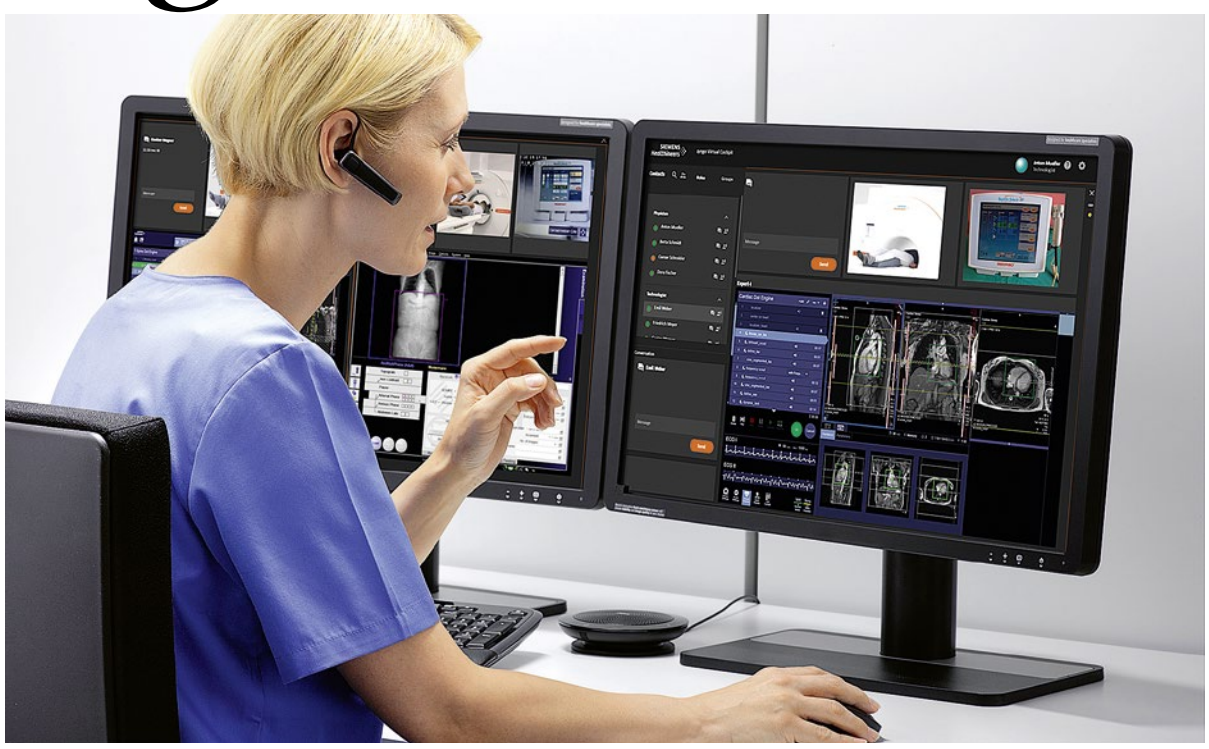
Dr Karl-Friedrich Kreitner is Professor of Radiology at the Department of Diagnostic and Interventional Radiology of Johannes-Gutenberg University in Mainz, Germany. He has published more than 200 articles in peer reviewed journals and 29 contributions to books.
He is co-editor of the books 'Cardiac Imaging: A Multimodality Approach' and 'Radiological Differential Diagnosis of the Heart and Great Vessels'.

He also spoke of a study conducted in the Institute of Legal Medicine in Hamburg following autopsies on the first 80 patients who died from Covid-19 in that city: 40% had thromboembolisms. Kreitner advised that, in the cases of suspected thromboembolism, timely imaging should be initiated.

'The main points are that cardiovascular involvement has a significant impact on prognosis for in-patients and it is absolutely necessary to control for D-dimer, fibrin degradation products, hi-sensitivity troponin and the NT-pro BNP during admission and the course of the hospital stay. This, especially for D-dimer and FDP; when they are elevated an anti-coagulative therapy should be considered and the amount – or whether it is a prophylactic or therapeutic dose - depends on the D-dimer value.' (MN)

Crisis brings opportunities to progress

Covid-19 boosts digitisation



Each crisis offers opportunities – a truism that's true nevertheless, as the current Covid-19 pandemic shows, which has taken many healthcare systems to the brink of collapse.

'The pandemic, horrible no doubt, has turned out to massively push our healthcare systems towards digitisation,' says Dr Christoph Zindel, Member of the Managing Board of Siemens Healthineers, supporting this diagnosis with evidence from his own company.

Covid-19 spurred technological developments in medical imaging. Whilst of secondary importance in the diagnosis of Covid-19 compared to PCR tests, imaging does have its place, particularly CT, X-ray and lung ultrasound.

As coronavirus was spreading, Siemens Healthineers 'with lightning speed' (Zindel) developed a software prototype based on artificial intelligence (AI) which can recognise and automatically highlight suspicious regions during a lung CT scan of Covid-19 patients such as the typical ground glass opacities. 'We provide this research prototype free of charge to our customers as a supporting tool for differential diagnosis of pneumonia and prognosis of Covid-19 patients,' Zindel reports.

Almost at the same time, Siemens Healthineers launched a new software package to support decision-making when assessing lung X-rays: the AI-Rad Companion Chest X-ray acts as a 'second reader' as it automatically characterises radiographic findings, including atelectasis and consolidations, which correlate with signs of Covid-19-induced pneumonia.

Around for years, telemedicine solutions are now being more widely used

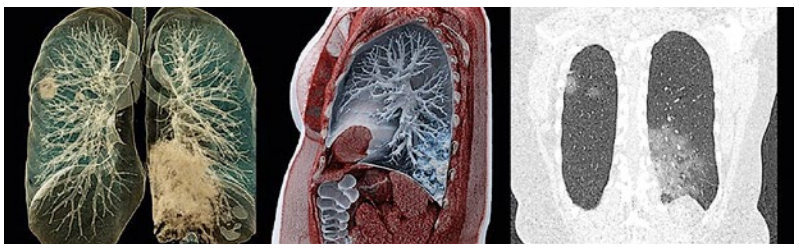
Covid-19 also drives telemedicine applications. As the demand for diagnosis of Covid-19 cases increases, healthcare providers are challenged to secure, or even ramp up, the capacity of expert radiologists, despite potential staff shortages from quarantine or sick leave. For radiologists, as for many other professionals, the home office has become the new normal, albeit requiring very different equipment such as remote scanning assistance. 'The application of this very useful technology has reached new dimensions', Zindel says.

Siemens Healthineers and the Clinic of Diagnostic and Interventional Radiology at the University Hospital Freiburg (UKF) launched a joint teleimaging project: Since the end of March the radiology technicians can perform MRI or CT scans either from a separate 'safe scanning room' in the clinic or from their home. Using the software package syngo Virtual Cockpit the technicians access the radiology systems via a secure network link to set up the MRI and CT scanner and to perform the actual scans. They can communicate with the staff on-site via conference speakers and video.

Patients prefer teleconsultations during lockdown

Teleconsultation numbers have also skyrocketed. 'A few months ago, at Mount Sinai Hospital in New York, 20 teleconsultations were conducted per day – today, it's 4.000,' Zindel reports.

Covid-19 is not at all the major issue as physicians deal with oncology and cardiology patients and take care of follow-up. 'The patients themselves are not particularly keen to visit a hospital since they fear infection,' Zindel points out. Instead they prefer out-patient facilities and are happy to collect health data at home, which they transmit electronically to their physicians.



Cinematic Rendering, lung of Covid-19-patients
© Siemens Healthineers / CHR Verviers East Belgium

Completely networked – the teamplay digital health platform

Siemens Healthineers' teamplay is a manufacturer-, system- and device-neutral digital health platform designed to connect radiology, clinic, out-patient facilities and the patients themselves. The AI-Rad Companion Chest X-ray also runs on this platform, which integrates more than 5,000 institutions in 60+ countries. A major teamplay component is myCare Companion, which supports patients with chronic diseases, such as cardiac insufficiency, by actively involving them in the treatment process and promoting compliance.

The Heart and Diabetes Center North Rhine-Westphalia (HDZ NRW) in Bad Oeynhausen is conducting a joint project with Siemens Healthineers based on the above technology: HerzConnect for patients with cardiovascular diseases. Mobile measuring devices, such as a mobile ECG, blood pressure meter and scales to measure body weight collect certain vital signs 24/7 and transmit the data via a smartphone app and a secure connection to the HDZ NRW for analysis. 'In Bad Oeynhausen the number of unscheduled patient visits dropped which is good news for hospital staff and patients alike in view of the current pandemic and infection risk,' Zindel points out, adding: 'Both parties recognise the advantages of decentralisation and virtualisation: the hospitals save time and chronically ill patients don't have to visit the hospital as often, which increases quality of life. This is here to stay – even after the pandemic has subsided.'

HerzConnect is a new managed care programme for cardiac insufficiency patients at the Heart and Diabetes Center NRW in Bad Oeynhausen, Germany © Siemens Healthineers

A broad portfolio – well-positioned

Asked about the future of healthcare digitisation, Zindel ventures an educated guess: the data recorded by mobile devices will be linked to the 'digital twin' being developed together with the Clinic of Cardiology at the University Hospital Heidelberg. This digital re-presentation of a patient's heart virtually shows structure, function and possible anomalies. This digital twin can support the diagnostic work-up as well as the simulation of drug-based therapies, or arrhythmia treatment.

But back to Covid-19: 'In the early days of the pandemic, CT and conventional X-ray played a larger role in diagnosing coronavirus but, over the course of time, PCR gained ground,' Zindel explains. In the USA alone 120 different antibody test procedures were thrown onto the market. 'It's a gold rush out there,' he exclaims. But not all that glitters turns out to be gold, he warns: 'Several tests were launched that did not meet quality standards.' However, Zindel's company, he points out, in no time received official clinical approval in the USA and Europe for Atellica Solution, a lab system with a throughput of more than 440 antibody tests per hour.

Zindel is confident: 'With its diverse portfolio Siemens Healthineers was and is well positioned for whatever the pandemic holds in store.'

In October 2019 **Dr Christoph Zindel** became a Member of the Managing Board of Siemens Healthineers AG. Born in 1961, he gained his doctorate at Goethe University Frankfurt and, in 1989, joined Siemens Healthcare as Segment Manager, serving in diverse management roles with increasing responsibility within the Magnetic Resonance Business Unit. From 2012 on he headed PETNET Solutions in Knoxville, USA, before joining Beckman Coulter to head the Haematology and Urinanalysis Business Unit as Senior Vice President, based in Miami, Florida. After his return to Siemens Healthineers in 2015, he served as Senior Vice President and General Manager of the Magnetic Resonance Business Line and became President of the Diagnostic Imaging business in 2018.

Remote-Scanning-Assistenz with Syngo Virtual Cockpit © Siemens Healthineers

Choose DL over ML algorithms

Radiomics strengthens breast

The field of AI-enhanced imaging provides radiologists with an unprecedented opportunity to shape patient care, a leading Austrian radiologist explained at ECR 2020.

Report: Mélisande Rouger

Workflow with radiomics starts with image acquisition and segmentation. When the region of interest is defined, radiomics analysis enables extraction of a large quantity of imaging features, and then to select, reduce, classify and model the data to answer a specific question.

'Machine learning or deep learning may be used at any step of the process and help in various aspects of daily practice,' said Katja Pinker-Domenic, a breast radiologist at the Memorial Sloan Kettering Cancer Centre, USA, and the Medical University of Vienna in Austria.

Current applications

When it comes to mammography, the most common use case for machine learning (ML) or deep learning (DL) is screening accuracy. Studies have shown that deep convolutional neural networks (CNN) achieve area under curves (AUC) of about 0.9, regardless of the framework. Researchers now want to take it one step further and are looking at performance of radiologists on mammograms with or without the help of artificial intelligence. AI support has been shown to increase sensitivity and there is a trend towards increasing specificity. 'When the radiologist is provided with a decision support system, performance improves, not reading time,' Pinker-Domenic said.

With ultrasound, the main application has been classification, to differentiate between benign and malignant masses. Ultrasound is recommended when a suspicious mass has already been spotted. However, to date, there are no guidelines that recommend using AI with this modality in clinical practice. 'More studies are needed to explore advanced DL methods and prove their usefulness,' Pinker-Domenic underlined. 'It's an area of interest.' A study by Barinov et al (Journal of Digital Imaging, June 2019) has shown that an FDA approved AI-decision support system incorporated in image analysis improved accuracy in breast cancer diagnosis for all radiologists, regardless of their level of experience. AI-enhanced MRI has by far been the most explored area, particularly in lesion detection. 'Research has shown that fully automated detection of breast cancer using CNN is possible and this is very encouraging, in particular with the trend of abbreviated MR protocols in breast cancer screening,' she added.

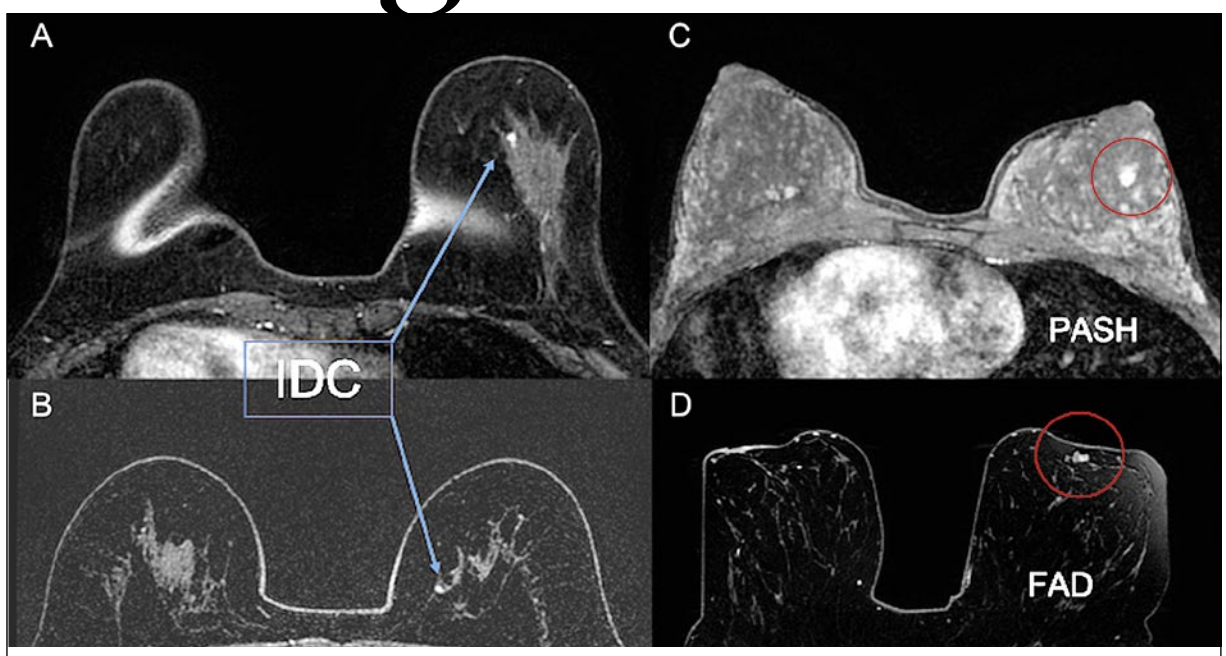
With CNN, the next step is classification. Authors of another study applied AI based breast lesion detection classification imaged to multiparametric breast MR protocol with ultrafast DCE-MRI, Tw2 and DWI. The researchers could show that the final AI system that incorporates information from all sequences showed significantly higher performance than DEC-MRI alone. When operating at the same sensitivity level as radiologists it was compared to, AI-enhanced MRI improved sensitivity and detected less false positives than humans, potentially sparing biopsy. However, in another study, radiologists did perform better than ML and DL, which performed better than ML (AUC: 0.88 vs. 0.81) for lesion classification. Radiologists should thus strive to use DL rather than ML algorithms, especially for complicated cases such as BRCA mutation carriers, Pinker-Domenic explained. 'We should identify cases in which we struggle, for example small enhancing masses in BRCA mutation carriers. These patients often undergo high-risk MRI screening and present with small tiny lesions that probably have a benign appearance but can be cancer. Our awareness level in this patient collective is already altered compared with an average risk of breast cancer,' she said. According to a recent study, the BI-RADS descriptors are not very useful to classify lesions, with a 53% diagnostic accuracy, 73% sensitivity and 42% specificity.

By contrast, radiomics diagnostic accuracy is almost 80%, and sensitivity and specificity are also higher (Figure 1). 'This shows potential for AI to be used as an adjunct tool, to spare unnecessary biopsies for benign appearing small breast masses. This can be very useful in these patients, who undergo repeated screening and biopsies,' she said.

Prediction and prognosis at hand

With AI enhanced MRI, radiologists can also try themselves at prediction and prognosis. Molecular subtyping with DCE-MRI has been studied extensively. Specific molecular subtypes seem to carry radiomics signatures that can be used to accurately classify those lesions with respect to receptors – the molecular subtype – with good diagnostic accuracy. These signatures have the potential to provide prognostic indicators that are derived from the entire tumour and that may be used to monitor tumour biology changes during treatment.

This function can be extended to contrast-enhanced mammography, which has the same underlying psychological mechanisms as MRI and can be used as an alternative when MRI is not available.



Axial first post-contrast bilateral dynamic MR images of two patients with benign-appearing small breast masses (A, B; blue arrows) in which biopsy yielded invasive ductal carcinoma and of two patients (red circles) categorised as BI-RADS 4 in which biopsy results yielded (c) pseudoangiomatous stromal hyperplasia and (d) fibroadenoma

A new standalone solution beats mammography

Abbreviated MRI protocol is superior

Is mammography still the best method for breast cancer screening? For a number of breast cancers, the latest scientific findings suggest otherwise. For more than a decade, Professor Christiane Kuhl MD, Director of the Clinic for Diagnostic and Interventional Radiology at the University Hospital RWTH Aachen, has researched the use of MRI in breast cancer screening. During a Bayer Healthcare webinar at the RÖKO Digital Congress the radiologist explained why she believes abbreviated MRI protocols to be a game changer which could, in fact, completely replace mammography for screening.

Report: Karoline Laarmann

Despite its overall success, mammography screening also continues to attract criticism. For one, it detects breast cancers which are prognostically irrelevant, resulting in overdiagnosis. Mammography also does not detect all breast cancers that are of prognostic relevance, thus underdiagnosing cases. "20-30% of breast cancers detected in women who participate in screening are not discovered during mammography screening but during the intervals,' Professor Kuhl points out. 'These interval cancers are basically nothing other than cases of failed early detection of fast-growing, and therefore prognostically relevant, breast cancers.'

The reason for underdiagnosis not only lies in the density of the glandular breast tissue but also in the tumour biology. As the detection of breast cancer in the mammography- or digital breast tomosynthesis image is based on the visualisation of architectural distortion, microcalcification or spiculated mass, it is particularly suitable to find luminal, i.e. less aggressive breast cancers, whilst biologically aggressive tumour types can appear in X-ray based images as ubiquitous, benign changes, such as cysts or fibroadenomas.

Prof Dr Christiane Kuhl has directed the Clinic for Diagnostic and Interventional Radiology at the University Hospital Aachen since 2010. Kuhl studied medicine in Bonn, the city of her birth (1966) and, in 2004, accepted a C3 professorship at the Department for Oncological Diagnostics and Interventional Radiology at the University Hospital of Bonn. Today, she is considered to be among the most renowned German breast cancer researchers. Her work has received numerous awards nationally and internationally. From her experience, Kuhl advocates the use of MRI for early breast cancer detection.

Improving prognosis with MRI

'We need a method for early detection which offers a sensitivity profile that meets the oncological demand and finds those cancers that are prognostically relevant,' Kuhl demands. In 2010 the professor of radiology already proved that MRI meets these criteria with the results of her multicentric EVA-Study. This compared the efficiency of different imaging procedures for breast cancer screening in women with increased risk in the family.

The study showed that MRI had the highest hit rate for tumours detected, and the interval cancer rate was zero. Kuhl presents a simple explanation: 'When we use MRI for breast cancer screening and use contrast medium, we do nothing other than visualising the angiogenesis and protease activity – tissue changes that directly correlate with carcinogenesis, cell proliferation and metastatic growth. This basically means that MRI is at the other end of the sensitivity spectrum compared to mammography. Or, put differently: the more biologically aggressive the breast cancer the more reliably it is detected with MRI.'

Fast and effective: Abbreviated MRI protocols

The reason that MRI is still rarely used for early screening, i.e. only for women with a high-risk profile, is mainly due to high cost and lack of availability. An abbreviated version of MRI, focusing on the essentials, can now provide relief. Kuhl and her team have developed a protocol which only consists of subtracted images acquired before and after the administration of contrast medium (FAST), which are fused into a projection image with maximum intensity (MIP). The results, first published in a study in 2014, astounded even Kuhl herself.

The diagnostic precision of the abbreviated MRI protocol was equivalent to that of the complete MRI protocol and was no less sensitive and specific. Furthermore, not only was the examination time short (three minutes) but so was the average time an experienced radiologist needed to determine whether breast cancer was present or not (2.8 seconds), and characterising an enhancement in an image also only took 28 seconds.

More than just an add-on – it works

Since then, many further international studies on the subject of abbreviated MRI protocols versus complete MRI protocol have been carried out,

t imaging

DWI has also shown ability to detect lesions and DWI radiomics signature might have the potential to provide a non-invasive, contrast agent-free method to assess tumour biology before, during and after treatment, Pinker believes.

'Luminal B and HER-2 enriched cancers seem to carry distinct radiomics features and may be used in this context.'

Another potential application is prediction of recurrence scores, which are currently assessed by genetic testing, a costly and often unavailable solution for many countries around the world. Imaging, when it is available, could offer an alternative with non-invasive testing.

'CNN achieved good class accuracies for prediction of low, intermediate and high-risk patients. CNN architecture can be trained to predict oncotype recurrent scores and offered to patients when genetic testing is not available,' Pinker suggested. Prediction of treatment response is also at hand with ML combined to multiparametric MRI, as the combination allows prediction of pCR and survival outcomes with high accuracy.

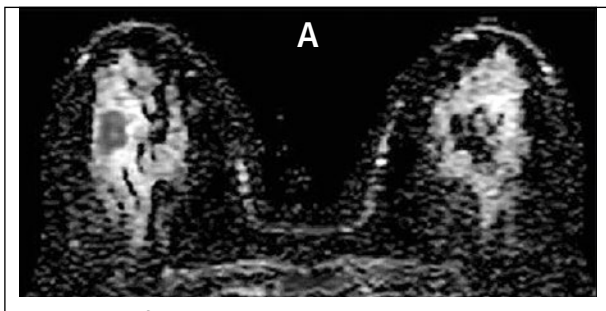
Allying radiomics with other data appears as a promising option. 'When we combine radiomics and other features, such as pathological stage or genomic type, we achieve the best performance. MRI can add in patient assessment for patient outcomes,' Pinker said.

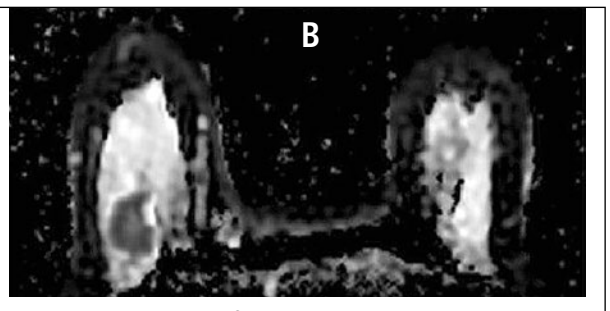
Researchers have also found that an image-based DL model to predict the five-year risk of breast cancer based on a single breast MR image from a single examination improves individual risk discrimination when compared with a state-of-the-art risk assessment model.

AI power is up for grabs but many challenges lie ahead, including the need for continuous study and the lack of a standard method for segmentation, feature extraction and selection and classification. 'We have small samples size and need further studies with large datasets and with subgroup analysis by patient group and/or tumour type. Independent testing is necessary for meaningful clinical implementation,' Pinker pointed out.

With ML and DL tools in breast imaging, radiologists have an unprecedented opportunity to better derive clinical value from imaging data and reshape the way they care for patients. 'Our greatest challenge will be to make our clinical partners adapt our AI enhanced imaging methods in their clinical workflow,' Pinker concluded. 'But I'm pretty confident think we will get there.'

Katja Pinker Domenic MD PhD is a radiologist and associate professor of radiology at the Department of Radiology, Breast Imaging Service, Memorial Sloan Kettering Cancer Centre in New York, and Department of Radiology, Molecular and Gender Imaging Service, Medical University of Vienna.

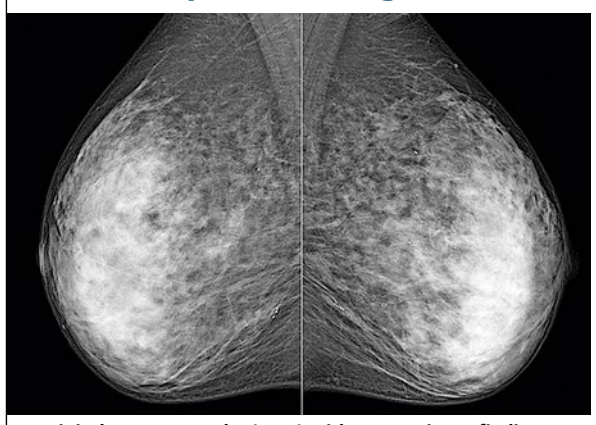




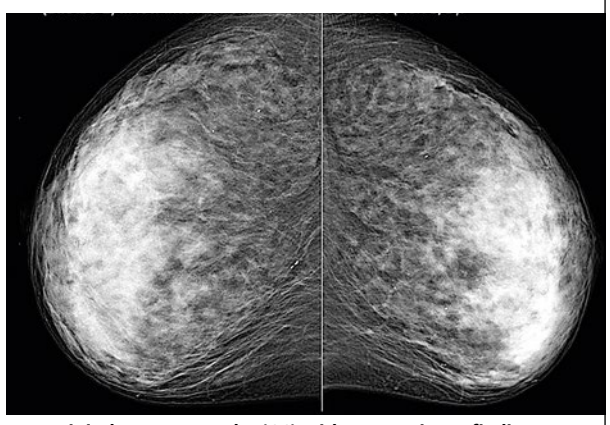
A: ADC map of 49-year-old patient with luminal A cancer in the right breast. B: ADC map of a 67-year-old patient with a luminal B cancer in the right breast. In a patient collective, radiomic signatures derived from DWI differentiated luminal A from luminal B cancers with an accuracy of 91.5 % when tumour segmentation was performed on the ADC map (89.5 % when segmented on high b-value DWI and copied to the ADC map). (DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient)

*** From: Radiomic Signatures Derived from Diffusion-Weighted Imaging for the Assessment of Breast Cancer Receptor Status and Molecular Subtypes**

Screening of a 64-year-old patient without family risk. Digital mammography without suspicious finding (BIRADS-2) in low intermediate dense breast (ACR 3/D)

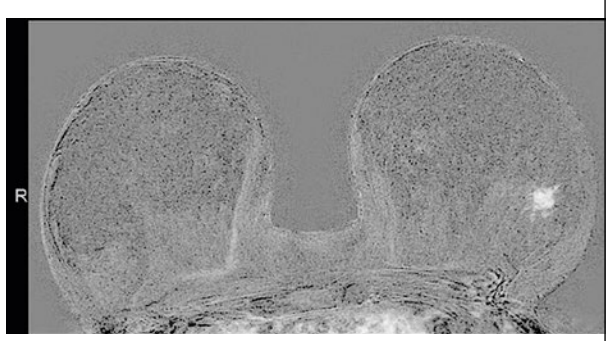


Digital mammography (MLO) without suspicous findings (BIRADS-2) in low intermediate dense breast (ACR-3/D)



Digital mammography (CC) without suspicous findings (BIRADS-2) in low intermediate dense breast (ACR-3/D)

MIP of abbreviated MRI: highly suspicous findings



FAST (first post contrast subracted) (= single-slice): MR-BIRADS-5

with all of them coming to the same conclusion: Abbreviated MRI protocol for screening works. But, does it work as a standalone tool for breast cancer screening?

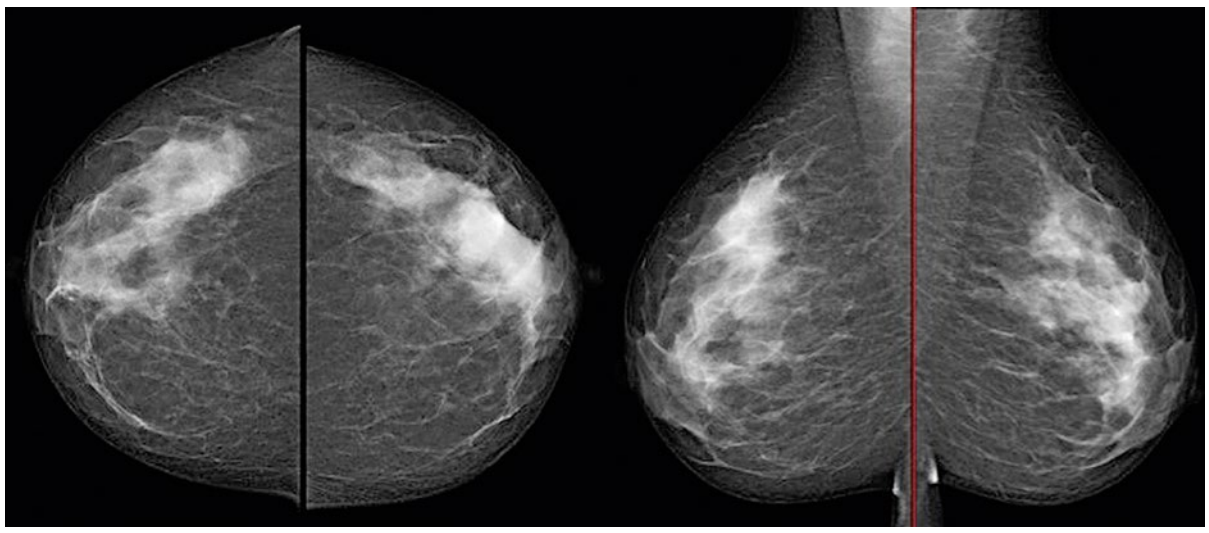
This question was examined in a study published in 2020 which compared abbreviated breast MRI protocols with DBT in women with dense glandular breast tissue. Both methods were used independent of one another.

It was found that the detection rate for invasive cancer for abbreviated breast MRI protocols was significantly higher than for DBT, i.e. 11.8 per 1,000 women vs 4.8 per 1,000 women. For Kuhl, the data means one thing: 'Abbreviated MRI protocols are not only an add-on method but a standalone solution that is superior to all other screening methods, independent of the individual risk of developing the disease.'

Algorithms must meet quality criteria

Deep Learning in breast cancer detection

A French expert in breast imaging looked at the latest DL applications in her field, screening their strengths and weaknesses in improving breast cancer detection.



Bilateral mammography

It is really important to understand which types of data sets need to be checked when evaluating an AI model for image interpretation, according to Isabelle Thomassin-Naggara, Professor of Radiology at Sorbonne University in Paris.

'The model is usually built on enriched data cohort with a high volume of BCs, ideally including all types of BC on mammography, speculated mass, run mass and cluster classification. Another data set must be used for internal validation,' she said.

The model also needs to be externally validated in another cohort with lower prevalence of cancer and possibly with more subtler cancers to improve its accuracy. Last but not least, the model must be evaluated with an independent data set with a prevalence that is representative of the screened population.

'Today, an algorithm needs more than one million mammographiesto truly demonstrate its efficiency. The development of dedicated platforms must be elaborated to build larger evaluation of data sets that are more representative of the population. All these steps can be performed retrospectively, but, before clinically validating a model, a randomised trial comparing the accuracy of a model with the radiologists' is needed,' she said. Incremental improvement in the 'area under curve' (AUC) is not directly translatable to improve patient outcomes in a clinical setting and it is uncertain which examined population a commercially AI system would flag as having more than 2% of malignancy requiring additional diagnostic workup in current clinical practice.

A costly mistake

'We learned from our experience of CAD in mammography that a product that promises new technologies too quickly can be a costly mistake later, by leading to find more false positives without improving cancer detection,' she said.

A number of studies have compared human vs. AI performance. A recent publication in the Lancet compared 25 studies and highlighted methodological limitations of validation studies of AI models, including the absence of calculation of number of subjects, absence of prospective design, presence of many statistic biases, absence of validation on independent samples and absence of comparison on the same population of AI model and human reading. (A comparison of DL performance against HC professionals in detecting diseases from medical imaging: a systematic review and meta-analysis, the Lancet, October 2019)

The Google paper on how its DL algorithm beat radiologists at detecting cancer made the news early this year and frightened a lot of radiologists. But this paper showed a number of flaws. 'When you look at this publicity, you can pick major errors. Look at the quality of the mammogram: even an expert radiologist would not be able to make a diagnosis correcly from such a low quality mammogram,' said Thomassin-Naggara, who pointed out further significant limitations, such as the methodology, which used two data sets with very different prevalence of malignancy – 1.6 % in the training cohort vs. 22.2% in the validating cohort. The vast majority of images in this study were acquired on Hologic equipment, so not representative of manufacturers' diversity. In addition, out of the +25,000 women included in the cohort, only 500 cases were used to compare the AI model with the human readers.

However, the main limitation was probably the poor performance of human readers overall, rather than a clearly spectacular performance from AI. 'Human readers' performance was very low and this could be improved,' she said. By contrast, another publication used two data sets with a normal prevalence of BC in screening populations in the US and independent validation cohorts in Sweden. 'Four AI models were tested and the results are interesting: No single AI model outperformed the radiologists. Using the AI models and human reading showed better outcome than using AI or the radiologist alone,' she said. These results are in line with previous work on an enriched cohort, which showed that radiologists' performance with AI was better than without. 'We have an increased specificity and sensitivity when the radiologist is helped by AI, and no limitation of time duration, which used to be a restriction with CAD,' she added.

Improving image acquisition and patient pathway

The challenge in these two applications is to lower radiation dose. Some software can do scatter correction without using anti-scatter grid, by identifying the structures that cause scatter and subtracts the calculated scatter. The dose-saving depends on breast thickness and structure. Another AI model has been developed to help the technician to achieve optimal positioning, by defining the right compression force and indicating the right exposure parameters.

After each exposure, anonymised data are sent to an external cloud database, which can analyse the final image quality of each diagnostic image and give advice on all acquisition parameters.

Optimising the patient pathway with AI-enhanced imaging delivers the ability to automatically evaluate breast density and quickly determine which patients will need ultrasound after mammography.

Up to now the different solutions to automatically assess breast density displayed low reproducibility and low performance, especially new BI-Rads lexicon because these softwares were based on segmentation.

Recently two DL softwares were optimised and demonstrated very nice agreement, reaching 99% for MLO and 96% for CC view to distinguish between fatty and dense breast. Another publication showed very good kappa agreement with radiologists (0.85)

The French radiology community reently highlighted the need to develop cloud software to automatically analyse daily images that can detect defaults or instabilities, to help medical physicists: decrease the analysis time during quality control (QC); create automatic analysis of QC criteria to simplify daily practice; offer automatic patient quality control assessment for technologists, for example blurring, position, compression, artefacts; and create a report for technologists' self-assessment.

'AI with DL will change practice and the place of imaging on the patient pathway. Imaging-based risk prediction of BC and biomarkers are potentially fantastic ways to personalise medicine and improve recommendations to our patients,' Thomassin-Naggara concluded. (MR)

Isabelle Thomassin-Naggara is Professor of Radiology MD at APHP Sorbonne University in Paris, France

Radiography: Correct patient positionin

Perfect musculoske

Dr Francis Zarb, a senior radiography lecturer at the University of Malta, outlined challenges in correctly positioning patients needing musuloskeletal imaging. During an interview with Sonja Buske he also offered a brief insight into the use of Artificial Intelligence (AI) in radiography today.

What are the challenges in positioning the patient for musculoskeletal radiography?

Zarb: The purpose of Radiography is to provide radiographic images using the lowest dose of radiation (ALARA) consistent with obtaining the required diagnostic information, taking into account economic and social factors. A radiograph can be compared to a shadow, in that it is a projection image whereby a 3-D structure is represented on a 2-D image with associated issues, such as super-imposition.

A radiographic image should faithfully reproduce the anatomical structures being examined, in terms of contrast and spatial resolution. Factors that need to be considered in producing a radiographic image include the technical aspects of the exposure and patient-related factors such as patient size. These may require changes in exposure factors to compensate for the differences in the thickness of the anatomy being imaged. Also important is the patient's co-operation, which may require the use of immobilisation aids and the use of the shortest exposure time possible together with effective communication. Image quality is not easy to define!

Does incorrect positioning affect radiation dose and image quality?

A poor quality image does not provide adequate diagnostic information and may lead to a missed or incorrect diagnosis. A poor quality image may also lead to a repeat examination, which in turn provides an extra unnecessary radiation dose to the patient.

Image contrast is the ability to differentiate between tissues based on their density, i.e. the difference in attenuation of the X-ray beam by the tissues being examined. Optimisation of image contrast is achieved through the appropriate selection of exposure factors, especially the kilo-voltage (kVp) and tube current (mAs) to limit scatter and image noise, both degra-ding image quality.

Scatter radiation can be limited in its production through compression (reducing thickness) and collimation (restriction of the size of the X-ray beam). Scatter can also be reduced from reaching the image receptor

The future of contrast agents

Gadolinium will stay a while longer

Manganese and iron oxide contrast agents can replace gadolinium-based contrast agents in a number of MRI examinations, but gadolinium remains a strong candidate when properly indicated, especially with AI-driven dose reduction and advances to increase relaxivity, a French expert explained at ECR 2020.

Report: Mélisande Rouger

Gadolinium-based contrast agents (GBCA) have been MRI companions for many years. In France, 30% of all MR examinations are still being injected with GBCA despite the recent safety crisis, according to Professor Olivier Clément, Head of Imaging at Georges Pompidou European Hospital in Paris. 'The crisis has not bended this use and I'm pretty sure this will not change in one day,' he said. 'Innovation in gadolinium based contrast media has been very active in the last 40 years,'

GBCA have been withdrawn from the market after a number of studies described nephrogenic fibrosis in renal patients and the presence of gadolinium deposition in the brain. Today only macrocyclic for non-specific enhancement and liver specific agents such as Primovist and Multihance are available.

Scientific societies have issued recommendations on when patients should be injected with gadolinium. 'We have to think twice before we inject a patient. Injection is not mandatory, but should be guided by clinical indication. Dose should be as low as diagnostically possible,' Clément said.

Researchers are actively working on solutions to get around current issues and three interesting scenarios are emerging.

Potential strategies include decreasing the dose then to use AI for contrast

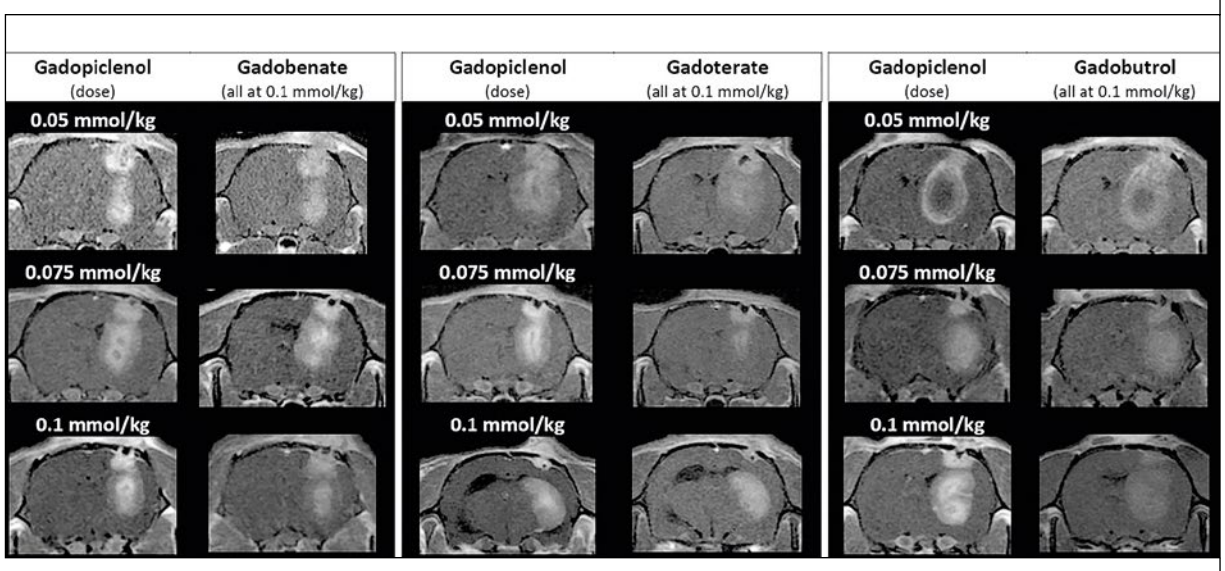
A first strategy is to decrease the dose and restore contrast with the help of AI. There is a lot of research on the topic in CT, and some papers have shown that AI can restore contrast between the liver and the tumour with one quarter of the dose. In MRI, studies have showed that contrast could be restored to the same quality as full dose with as low as one tenth of the dose.

'That's a very interesting development. New imaging processing algorithms will enable restoration of the contrast obtained with lower doses of gadolinium chelate,' Clément said. 'Still we're going to need to inject.'

Creation of new gadolinium products

Another way to go is to create new gadolinium products with increased relaxivity and low protein binding. This has been done in the past with different contrast media, such as Guerbet's P792, which allowed increasing relaxivity while interacting with water molecules. Today, researchers are working on a new compound using the same idea to increase relaxivity, in order to lower the dose to be injected. A number of studies have recently shown that relaxivity with Gadopiclenol, a macrocyclic GBCA, could be at least twice as high as with Multihance, and clinical trials in humans are undergoing. (Radiology. 2020 Jan; 294(1):117-126. doi: 10.1148/radiol.2019182953. Epub 2019 Oct 29).

Professor Olivier Clément MD PhD, is Head of Imaging at Georges Pompidou European Hospital in Paris. He is also Chairman of the Imaging Informatics and Clinical Research Department and Chairman of the CIRTACI (working group on Contrast Agents of Société Française de Radiologie).



Changing gadolinium to a contrast metal, such as manganese or iron

A completely different and interesting track to explore is to change gadolinium to another contrast metal. Manganese and iron based contrast agents are two strong candidates to replace GBCA, Clément explained. 'We can use iron oxide particles, for example in liver imaging. These agents can also be useful to do cellular imaging, when these compounds are integrated with cell culture. We foresee potential uses with iron oxide compound agents in cellular tissue therapies'

So far, iron oxide nanoparticles contrast agents have been 'kind of disappointing' for liver applications and have been withdrawn from the market. Iron oxide nanoparticles are currently only being used to treat iron deficiency. Potentially contrast agents with ferric oxide (e.g. Resovist) could be used as well, but these products have not yet been marketed.

Problem: Long timeframe

A major issue when developing contrast agents remains the long timeframe that unfolds between identification of a medical need and the final approval by regulatory bodies. 'It takes about ten years to obtain regulatory approval for contrast agents,' Clément observed. 'This is long compared with the very fast timeframe of technical development of MRI machines.'

Challenges to develop new agents are not just regulatory, but also financial, with long and expensive clinical trials, and issues of chemical scale up and the final pricing. 'It's a big challenge for a company to invest in a new compound,' he pointed out.

The future of gadolinium-based contast agents is promising

Given the current complexity, the future of GBCA is promising. "

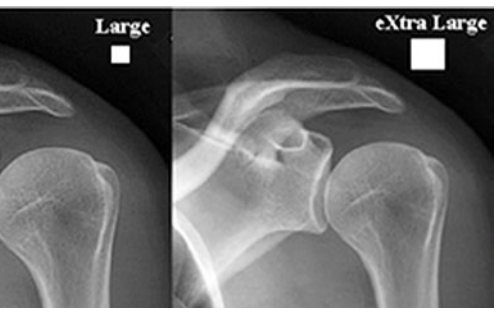
'Economists foresee that we will still be using gadolinium to some extent and the market is set to grow in the near future,' Clément confidently predicted.

'I'm pretty sure we will use, for a long time, our old macrocyclic contrast agents in MRI, but we will have to optimise dose and indications.

'We might need higher relaxivity agents,' Clément continued, 'or we might need to decrease our dose and restore contrast with AI algorithms,' he concluded.

g is critical

letal imaging



The effect of focal spot selection on image sharpness during shoulder radiography

through the correct use and positioning of ant-scatter grids.

Spatial resolution is the ability to differentiate between two small structures of the same density based on their position is space. In this context, a radiographic image should faithfully represent the location, shape and size of the tissue being imaged. Spatial resolution is a function of geometric factors (magnification, distortion, characteristics of the X-ray tube), motion and artefacts. One can optimise spatial resolution by placing the anatomical structure as close as possible to the image receptor, correctly positioning the patient, removing any opacities from the area being examined and using the shortest exposure times possible.

Does artificial intelligence (AI) provide technical features that help with positioning?

AI plays a beneficial role in radiography as a clinical decision support tool for appropriate justification of radiographic examinations. Furthermore, it optimises imaging workflows by performing automated quality assurance and it may offer indications for repeat examinations in the event of poor quality images.

AI also supports image interpretation among others. But, radiographers must understand how algorithms arrive at decisions and at probability errors within these decisions, to enable effective communication of findings to patients. With such developments in machine learning and AI systems within medical imaging, radiographers are required to adapt their imaging practices to ensure that this new technology is implemented, used and regulated appropriately to maximise benefits to patients.

Radiography educational programs must be regularly reviewed, to support the development of the appropriate skills fully within the profession.

Dr Francis Zarb is a full time senior lecturer at the University of Malta. His lectures focus on imaging of the head and spine, imaging in trauma, paediatric and elderly imaging, and the clinical applications of CT and MRI. Along with his research on radiation dose and image quality optimisation, for the past 25 years he has been responsible for the clinical placements of radio-graphy students. He is ECR2021 Co-chair of the Radiographers Subcommittee.

A new technique to understand metabolic pathways

Mass spectrometry-based metabolomics

Laia Castaño-Espriu is a final year PhD student at the University of Strathclyde in Glasgow under the supervision of Dr Katherine R. Duncan, with a particular research interest in metabolomics, actinobacteria and drug discovery.

Mass spectrometry-based metabolomics has emerged as a powerful tool to help study chemical ecology. Recent advances in the technique make it possible to study microbial interactions from complex communities.

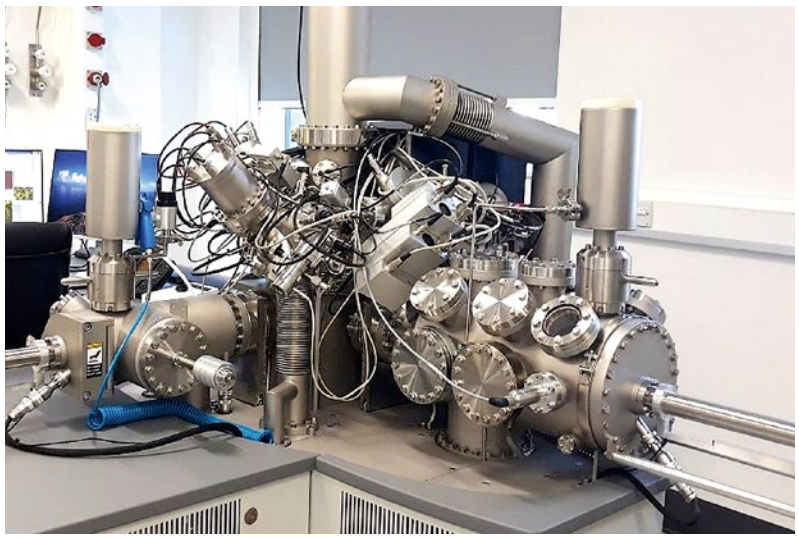
Laia Castaño-Espriu outlined the role and benefits of MS in this context in her presentation 'Analysis of microbial ecology by mass spectrometry-based metabolomics techniques', at the joint meeting of the German Society for Hygiene and Microbiology (DGHM) and the Association for General and Applied Microbiology (VAAM) in Leipzig, Germany this March.

Castaño-Espriu explained that the bacterial order Actinobacteria is responsible for the production of 65-70% of microbially-produced specialised metabolites with diverse biological activities, but it is estimated that only 10% of biosynthetic genes clusters encoding the production of these specialised metabolites are transcribed under normal laboratory conditions.

Microbial competition enhances chemical diversity

'It's been observed that microbial competition enhances chemical diversity as an ecological advantage,' she said. 'Therefore, the study of bacterial competition is key in understanding the ecological role that secondary metabolites pose to microbes and in understanding the induction of cryptic biosynthetic gene clusters.'

As a final year PhD student at the University of Strathclyde in Glasgow, Castaño-Espriu's project is based on the analysis of microbial interactions by co-cultivation and MS-based metabolomics, with a particular focus on Actinobacteria that has been isolated from the marine environment as a potential source of novel chemistry.



Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) equipment

The analysis of these interactions by LC-MS revealed the production of metabolites that were co-culture specific and they found that several interactions not only enhanced chemical diversity, but also inhibited the growth of several clinically relevant pathogens, she explained. 'Furthermore, we could gain a better understanding of the chemical ecology during bacterial competition, where changing conditions aggravate the complexity of these interactions. Therefore, we demonstrated that MS-based metabolomics is an exciting strategy to study microbial ecology and to prioritise novel chemistry.'

Metabolomics approaches – referring to the study of the complete set of metabolites found in a cell, tissue, organ or organism – in general are applied to compare the chemical profiles of different experimental groups to find out the chemical response to external stimuli such as environmental stresses, she explained. 'MS-based metabolomics approaches in microbial ecology enable the understanding of microbial interactions in complex communities. Metabolomics allows the analysis of those metabolites that are produced during microbial interactions, therefore, providing a snapshot of the ecological role of these metabolites in the producers. This allows the understanding of biological questions such as Why are certain metabolites produced under specific conditions?, she pointed out.

By studying the secondary metabolism of organisms in complex communities and understanding the role of interesting metabolites, Castaño-Espriu continued, it is possible to gain greater insights in the correlation between phenotypic traits and microbial interactions.

Identification of potentially significant metabolites

Her work utilises Time-of-Flight Secondary Ion Mass Spectrometry (ToF-SIMS) and Liquid Chromatography Mass Spectrometry (LC-MS). The MS-based metabolomics studies follow the steps of sample collection and preparation, generation and acquisition of MS data (metabolic profiles), data processing using a deconvolution software such as MZmine, and statistical analyses. 'This approach,' she said, 'enables the identification of potentially significant metabolites belonging to the groups of interest, therefore, prioritising these for chemical identification and further experiments to understand the underlying mechanisms of the metabolic pathways.'

MS-based metabolomics techniques offer advantages in fields including the effect of drugs at a metabolite level; drug development; the study of diseases such as cancer, nutrition science, toxicology analyses to natural products; and chemical ecology research. 'Therefore,' Castaño-Espriu added, 'MS-metabolomics represents a multi- and interdisciplinary approach that can be used in different fields to understand metabolic pathways.'

Metabolomics, she added, aims to deliver more rapid and reliable analyses combined with more economical methods, data standardisation and the sharing of more MS data through online databases.

Recent applications of metabolomics include disease biomarkers and drug development, with a significant increase in the use of MS-based metabolomics observed in the area of microbial ecology in the last decade.

Compared to other techniques, Castaño-Espriu believes that metabolomics is the best approach to accelerate drug development as it is low-costs and also rapid and effective. 'This effectiveness makes a meta-bolomics approach ideal for other life and medical sciences.'

She feels it will become necessary to develop new technologies that offer greater sensitivity and spatial resolution to improve data quality, and to create databases with more MS data coverage to facilitate metabolite identification.

Another challenge lies in data variability based on sample preparation and the sample matrix among other factors. However, she believes the development of new instruments and new methods will aim to overcome this limitation. (MN)

Detectable: paediatrics' tiniest

Device makes veins visible

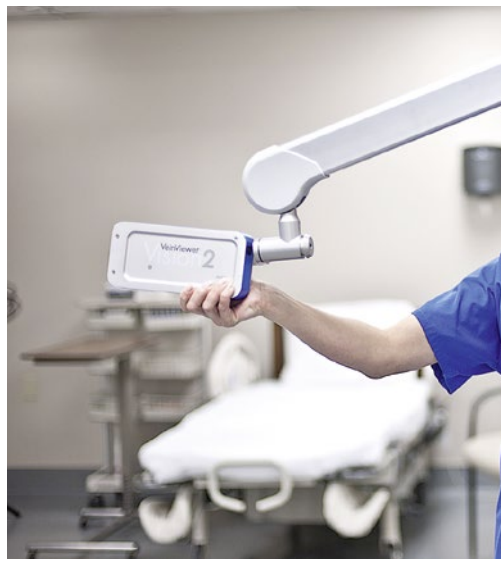
The device VeinViewer® from Christie Medical Holdings benefits from advanced near-infrared light technology before, during and after venipuncture and venous access, Greiner Bio-One reports. 'VeinViewer helps you to improve the success rate of the initial venipuncture and increase patient satisfaction and safety.'

'Harmless near-infrared (NIR) light is directed towards the patient's skin,' the firm explains. 'Haemoglobin in the blood absorbs the NIR and the surrounding tissue reflects it back to the device, where the data is processed into an image, colour is added and the image sent back to the skin to provide a real time visualisation of the blood vessels and patterns up to 10 mm below it. HD technology with digital full field help provide the clinician with clear, sharp imaging to support routine healthcare work when vein conditions are poor.'

The hand carried VeinViewer Flex – for use in emergencies 'packs the latest advances in superior vascular imaging into a handheld, mobile package,' the company reports. 'VeinViewer can help deliver faster venipuncture procedures on your difficult patients through greatly improved first stick success. Flex gives you revolutionary HD views in real-time, so you have the best view of vasculature procedures pre-, during and post-access.'

Flex runs on Fast Swap Battery and AC power so there are no concerns about a down device and durability meets the busiest use. Durability meets demand in the busiest use in, for example, vein care centres, and departments for oncology, geriatrics, dialysis, casualty, emergency/triage, etc. There's a stability to aid hands-free operation, and the Flex Imaging Unit is ergonomically designed for simplified procedures. The standard Universal Mode provides HD and Df2 projection technology, a clear and accurate view of superficial vein patterns in real time, even in remote locations, Greiner Bio-One points out.

VeinViewer Vision2 is a mobile imaging unit with an arm reaching up to 1.35 metres, attached to a trolley for easy transportation between beds or phlebotomy chairs. The ASSESS Imaging Suite of software is available only on VeinViewer products. 'The choice of various



From over-promising to a reality check

Digital pathology going Dutch

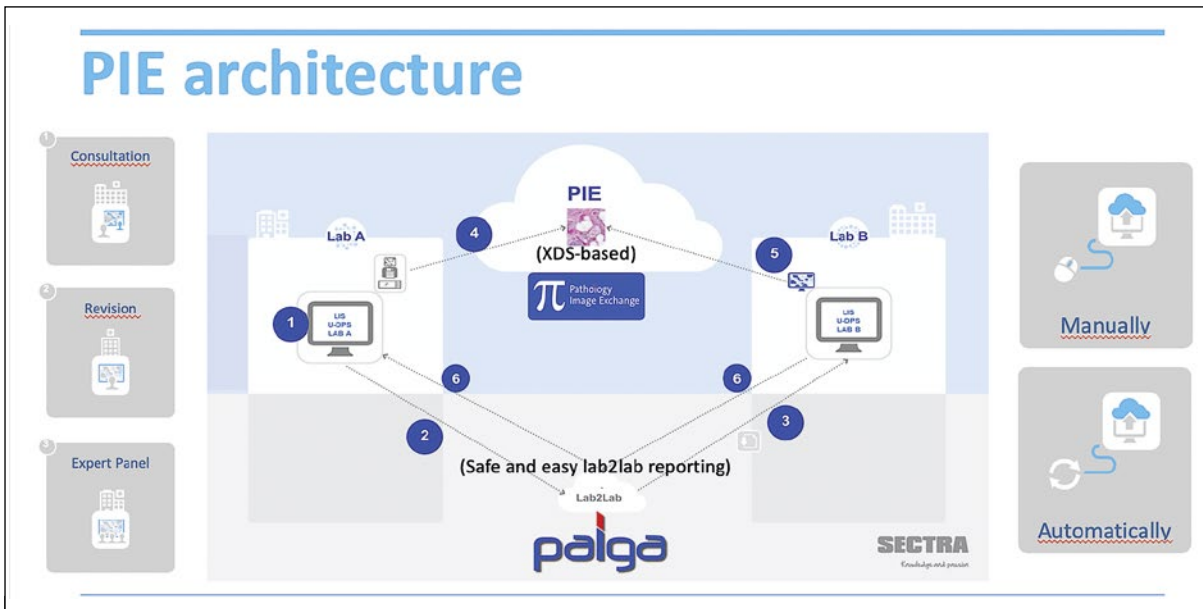
Katrien Grünberg is Professor of Pathology and chairs the Department of Pathology at Radboud University Medical Centre in Nijmegen, the Netherlands. She is also Past President and current board member of the Dutch Society of Pathology.

Almost five years ago, the plan to implement a wide-ranging digital pathology approach across the Netherlands began to take shape.

As more labs across the country acquire digital pathology capability, with steps to create a strong and accessible image repository and a national image exchange platform, one of the project leaders, Professor Katrien Grünberg, offered an update and spoke of some challenges that still lie ahead.

In a keynote presentation, 'Digital Pathology going Dutch' at the recent Digital Pathology and AI Congress in London, she also touched on the experience in Nijmegen, where she is Professor of Pathology and chair of the Department of Pathology at Radboud University Medical Centre (UMC). 'Sometimes we over-promise and sometimes we have to have a reality check,' Grünberg told delegates as she outlined the healthcare landscape in the Netherlands regarding pathology with 90 hospitals, 50 pathology departments with 350 pathologists and 27 molecular facilities.

Of the 50 labs, 16 had scanners in 2017, increasing to 23 this year, leaving 27 labs still without scanners, Grünberg pointed out.



Key trends and challenges

Key trends in the country are more molecular diagnostics; digital pathology and AI; and increased scale as well as a move towards specialising. All these trends are 'game-changers' by themselves, she said, but in addition, they interact too.

Whilst Radbound UMC has a strong reputation for computational pathology, she acknowledged bringing it into everyday practice has not always proved straightforward.

Grünberg outlined how, four years ago, Radboud made the decision to move to digital pathology, wishing to start the roll-out in 2019. 'We had hoped to have our first algorithms into practice in 2020, but that is now more realistically going to be 2021,' she continued. 'While digitising is all connected to machines, on the people side the technicians and pathologists have been very active in redesigning the workflow and integrating digital pathology into a highly-tuned laboratory workflow.

'They are right in the middle of living through the transformation process. It's hard work and requires perseverance and endurance and you have to believe that, in the end, it will revolutionise your work. While you keep going you also still have to provide a quality and efficient service for patients.'

A core component of the march towards digital pathology in the Netherlands has been to establish a Pathology Image Exchange (PIE) at a time of more lateralisation in the country's healthcare, with patients being treated in different locations and often closer to home.

From pathology focus groups, an aspect that emerged was that whole slide imaging was the way to go to build the national imaging platform.

'The requirement to be vendor neutral was key,' said Professor Grünberg. 'We had to make it available to all pathology departments in the Netherlands.'

She explained the PIE architecture was designed with the direction of flow of images and reports taking different routes to come together at the receiving end and also a manual and automatic workflow, for high volume of consultation.

Work in progress

Although moving forward, the project is still 'a work in progress', Grünberg pointed out. It remains costly and complex for labs to link and, at this stage, only seven labs are connected to the PIE at a time of rapid market developments and increasing costs.

In addition, DICOM standard is not as standardised as hoped with a 'to do' list that still includes a drive to connect labs to PIE and implement Lab2Lab connectivity, tackle DICOM issues and costs.

Artificial intelligence (AI) has an important role to play, with deep learning a powerful tool with computer aided quantification and grading, with AI eventually becoming an integral part of the overall assessment process.

One of the big challenges for the computational group was in getting good data sets to lead to good algorithms. 'A good way to do that is to team up with other hospitals to build up a really good archive,' Grünberg continued. 'You have to team up to create a large repository, especially for rare diseases.'

The dream is for a flexible data repository within the platform where participants can contribute and access data and while secure data storage has not been a major problem, she conceded there have been challenges around secure data transfer.

Yet at Radboud, and across the Netherlands, there remains a determination to rise to the challenges of promoting AI development by organising access to data. (MN)

modes ensures optimal visualisation of veins for more control and better assessment of each individual patient,' Greiner Bio-One continues, adding that the system is also good for seeing veins in small paediatric cases or sclerotherapy patients.

The system is HIPAA compliant, takes up to 200 static .PNG images of the blood pattern for export to EMR documentation. It also can reverse the colour of veins within the image field for further image customisation, and can resize – Greiner confirms that a choice of up to three window sizes is a great feature for paediatric patients.

Details: www.gbo.com.

High-capacity digital image analysis

Spatial statistics extract subvisual features

Spatial analytics offers greater clarity in the assessment of tumours beyond routine microscopic analysis, Mark Nicholls reports.

High-capacity digital image analysis enables new methods of spatial statistics to extract features not immediately distinguishable by visual inspection. These subvisual features reflect complex properties, such as intratumour heterogeneity and have the additional benefit that they can target specific compartments in the tumour micro-environment.

Advances in this field were detailed in a recent webcast organised by Global Engage and sponsored by Indica Labs, which focused on research that has identified novel prognostic signatures using new spatial analysis and machine learning to measure tumour-immune cell interactions within the tumour immune micro-environment.

In his presentation 'Assessment of Intratumour Heterogeneity and Tumour/Host Interaction using Spatial Analytics', Arvydas Laurinavicius, Professor of Pathology at Vilnius University, outlined his team's work on spatial image analytics work based on hexagonal grid subsampling of digital image data.

He highlighted how machine reading can generate much more data on the proliferation rate and its spatial heterogeneity in breast cancer compared to conventional microscopic assessment. This enables much richer data sets for further analyses, generated from routine pathology slides.

He further explained that subsampling of image analysis data into hexagonal grid tiles provides good opportunities to appraise the tumour texture, the so-called Haralick entropy, which estimates the spatial heterogeneity or 'disarrangement' of tumour proliferation rate.

Two analytical models

'We have developed two analytical models based on hexagonal tiling of image analysis data,' Laurinavicius added. 'They enable quantification of subvisual features of intratumor heterogeneity and tumour/host interaction; furthermore, these two methodologies can be combined for integrated prognostic models.

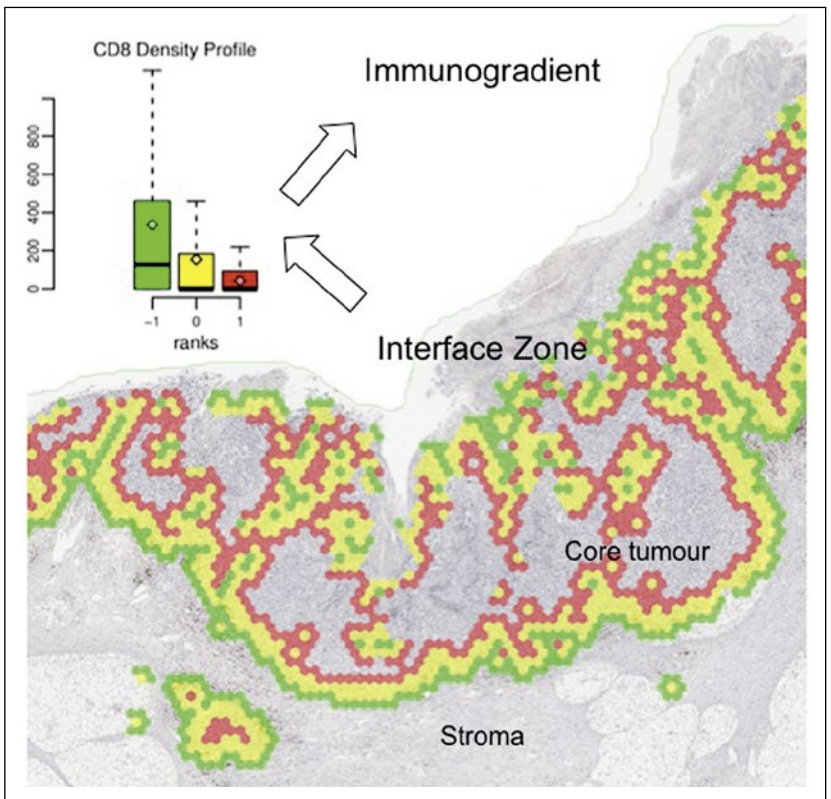
'We compute spatial entropy of biomarker expression based on the co-occurrence matrix built from all six neighbours to each hexagon.'

Beside the Ki67 heterogeneity indicators obtained by hexagonal tiling, which outperform proliferation rates, he said it is possible to visualise and measure 'Pareto hotspots', which represent the 'hottest 20%' of the proliferative area in the tumour.

'We have published and unpublished which indicate that heterogeneity measurement is more informative than the level of biomarker expression itself, even in the hotspots,' he explained.

In appraising tumour-host interaction, Laurinavicius stressed the importance of looking for best methods to measure tissue immune response features.

A well-established 'Immunoscore' system has been shown to provide independent prognostic value in colorectal cancer; remarkably, assessment of the tumour immune microenvironment may significantly improve the prognostic and predictive power of testing in solid tumours, compared to current clinical routine. This will guide individual therapy decisions, in particular, to benefit from new cancer immunotherapy options.



The Interface Zone between the core tumour and stroma is represented by the ribbon of coloured hexagons: red – tumour aspect; yellow – tumour edge; green – stroma (host) aspect. CD8 density profiles are extracted from the corresponding interface zone ranks; they are further used to compute immunogradient indicators. The analysis is performed on immunohistochemically stained colorectal cancer tissue section.

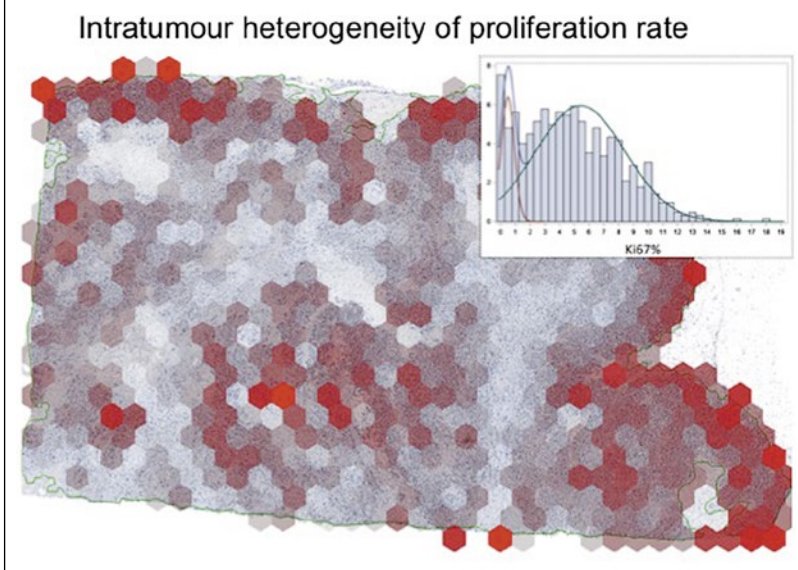
named 'Immunogradient'. Several indicators were used to quantify this, including centre of mass, which is a quantitative feature that tells whether these cells are 'willing' to enter the tumour or stop at the edge.

'We can optimise the method for each type of tumour,' Laurinavicius explained. 'For breast cancer, we need a broader zone to collect more data to compute Immunogradient indicators, as there are less lymphocytes.

'We tested the prognostic value of these indicators. In all prognostic models we have the Immunogradient indicators as independent predictors along with lymph node involvement data in breast cancer and T stage in colorectal cancer.

'Looking at patient survival probabilities in both cancer cohorts, we see that a good prognostic stratification can actually be achieved by any of the immunogradient family indicators.'

One feature noted in early hormone receptor-positive breast cancer patients was that five years after surgery all patients do quite well with a 92% survival rate but after 10 years there is a dramatic diver-



The hexagonal grid overlaid in breast cancer tissue section, stained on immunohistochemically for Ki67 (proliferation marker). Higher intensity of red shading of the hexagons represents higher local proliferation rate. This data is used to compute texture and bimodality indicators to quantify intratumour heterogeneity of proliferative activity.

In another example, Laurinavicius pointed to the value of 'tissue phenomics' to predict prostate cancer recurrence, by the appraisal of immune cell densities and distances within automated tumour gland/stroma outline and fixed zones around the outline.

Focus then turned to a recently published study in breast and colorectal cancer patient cohorts and novel Interface Zone Immunogradient indicators computed from tumour infiltrating lymphocyte density profiles across the automatically sampled tumour/host front line.

'We looked at tumours with a slightly different approach,' Laurinavicius continued. 'If you want to identify the invasive margin, the question comes as to where should you draw the "invasion line"; you can do it manually, or automatically, but should you outline every gland in every case?

'If you consider where the fight happens between the host and the tumour, it is a rather irregular area. We explored the concept of extracting an interface zone, rather than just a margin, or a ribbon, of a fixed width between high-level visual features.'

A natural question, he said, was whether the hexagonal tiling could be utilised to detect these interface areas. 'It took us a while but we implemented this procedure based on single CD8 immunochemistry and digital image analysis.'

For the digital image analysis, the researchers utilised the Indica Labs Halo AI to automatically classify the tissue sample and quantify cells.

From the image analysis data they developed a set of rules based on the tissue content within each hexagon, and its surrounding hexagons, to estimate the probability of each hexagon being at the interface. The tumour/stroma edge can then be extracted as those hexagons with high 'interface-ness'.

The interface zone which reaches both into the tumour and host tissue was established around the edge by ranking hexagons according to their distance to the tumour/stroma edge.

Example: colorectal cancer

In a practical example for colorectal cancer, the interface zone was detected and ranked automatically and immune cell densities in each rank was used to construct an interface profile of the biomarker density.

This reveals the immune cells' 'gradient towards tumour' and was gence of the two probability curves: high Immunogradient patients maintained 87% survival, while low Immunogradient patients had 55% survival after 10 years.

'Such knowledge about immune-response properties, obtained from the surgically excised tumour, which predicts long term survival, suggests that these patients should be monitored more closely and could benefit from immunotherapy during the course of their illness,' Laurinavicius added.

Effective combination of prognostic models

The prognostic models based on tumour heterogeneity, interface and gradient, can be effectively combined, he said.

Finally, Laurinavicius pointed out that frequently spatial heterogene-

Arvydas Laurinavicius is Professor of Pathology at Vilnius University, and Director of the National Centre of Pathology, affiliated to Vilnius University Hospital Santaros Klinikos, in Lithuania. His key areas of interest include renal pathology, digital pathology image analysis, computational pathology, health information systems, standards, testing of cancer biomarkers in tissue, and multi-dimensional disease models. He is currently leading a project funded by the European Social Fund, project No. 09.3.3-LMT-K-712-01-0139 under grant agreement with the Research Council of Lithuania.

ity indicators of tissue biomarker expression out-performed the prognostic power of the level of the biomarker expression. 'We found that the gradient at the interface out-performs absolute or relative immune cell density indicators obtained from tumour microenvironment compartments. Furthermore, spatial immunochemistry-based models often are independent of conventional clinical or pathology features; they have good statistical powers, especially if one quantifies the biomarkers by appropriate indicators.'

The webcast also featured a presentation from Doctoral Student Ines Nearchou from the University of St Andrews, Scotland, on 'International validation of a novel spatial immuno-oncology prognostic model in stage II colorectal cancer', and from Dr Kate Lillard Tunstall, Chief Scientific Officer with Indica Labs on 'Spatially-resolved profiling of the tumour immune microenvironment' who also outlined her company's HALO spatial analysis tools.

Overcoming the barriers to AI in digital pathology

'You can't do AI on glass slides'

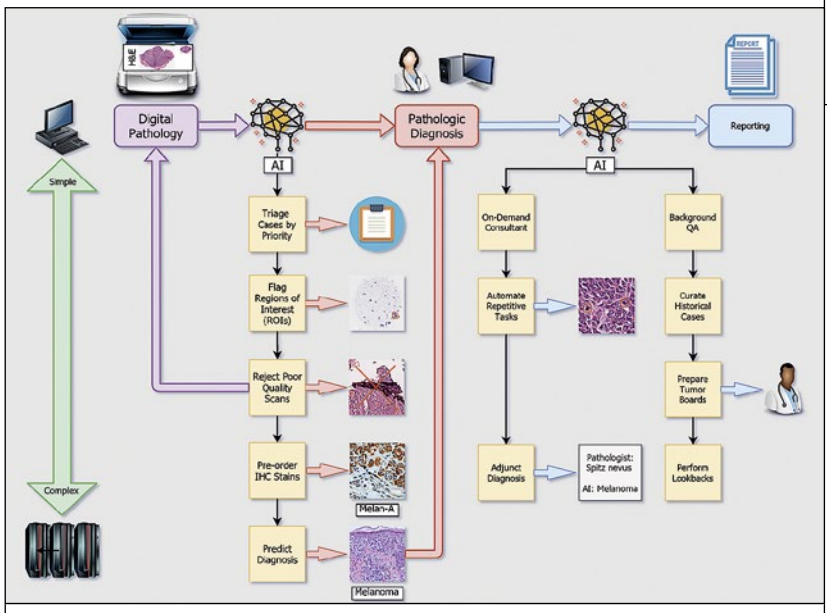
As Artificial Intelligence continues to impact on the development of digital pathology, potential users are still slow to implement key enabling technologies to harness the benefits, according to Dr David McClintock, who will detail critical steps for pathology departments to transition practice from glass (analogue) to digital (whole slide imaging) and embrace AI, to the 6th Digital Pathology and AI Congress: USA, online on 19-20 November.

'To take advantage of any of the current and future artificial intelligence/machine-learning algorithms available for anatomical pathology, you need to have your slides digital. Literally, if you are not performing whole slide imaging, then you won't be doing an AI,' McClintock explained, speaking with European Hospital ahead of the conference.

While his presentation 'If you don't scan yer slides, you can't have any AI!' acknowledges that interest in AI in pathology has grown, implementation of AI's enabling technology is slow, with few pathology practices adopting a completely digital workflow.

Significant barriers remain

McClintock, Associate Chief Medical Information Officer and Director of Digital Pathology at the Michigan University said, barriers against adoption of digital pathology remain, including the upfront capital costs of whole slide imaging (WSI) devices, continued incremental operational costs of storage, and image management system licensing. He added that WSI systems have been slow to obtain regulatory clearance in Europe and the USA: 'WSI and image management system vendors are only recently adopting the Dicom medical imaging standard, making inter-operability between different scanners and software much more feasible. 'Finally, anatomical pathology (AP) workflows are practically a century old or more – digital pathology, especially combined with AI, represents a massive change in how pathologists view, assess, and interpret slides. In combination, these are fairly daunting issues to overcome to implement digital pathology, before you begin to talk about adding in AI.'



To address this, pathology departments should define a primary business/use case for wanting to adopt digital pathology and document workflows to understand what resources will be required when making the transition.

Key questions include understanding the case/slide volume, how these slides will be separated out and scanned in the histology lab, who will do the scanning, and what displays and workstations will be used for digital sign-out.

Yet, McClintock maintains there are clear benefits for pathology going digital. 'It opens up a plethora of technological innovations for anatomical pathology that would be difficult to implement in our current analogue/glass/microscope world.' 'Once slides and cases are digital, you can aggregate clinical data and apply machine learning algorithms to your AP workflows.'

Having slides digital also enables easier second opinion consultation, access to subspecialty pathology experts, and telepathology. However, there are also pitfalls, including reliance on AI, not having algorithms for all diagnoses, and variable and inadequate access to AI because not all practices can implement it.

McClintock will also explore how the digital pathology adoption argument in the AI-driven world needs to be reframed. 'The digital pathology argument used to be mainly based on internal laboratory or lab system improvements,' he said. 'With AI, the argument for digital pathology becomes more imperative – you can't do AI on glass slides and once AI becomes standard of care for pathology, then digital pathology will become just another set of instrumentation a lab must implement to meet regulatory and patient care needs.'

Dr David McClintock is Associate Chief Medical Information Officer (ACMIO), Director of Digital Pathology; Associate Director, Pathology Informatics; and Associate Professor (Pathology) at the University of Michigan. His research interests include digital pathology workflow, implementation of digital pathology and AI in pathology and the clinical laboratories, and regulatory aspects of digital pathology.

The route towards greater acuity

4K enriches detail

4K is the latest video standard, yet this provides notably high-quality image viewing. In the operating theatre, this technology is a particularly quality-enhancing achievement, Rein Medical underlines.

What is 4K? Generally there are two standards, which are often mixed up; one is 4k and the other UHD. The slight difference lies in resolution. The UHD resolution is 3840 x 2160 pixels, which equals four Full HD Videos. 4K is 4096 x 2160 pixels. Both standards offer a much higher resolution, compared to Full HD Video – and this is the actual benefit: a totally new level of detail.

Why 4K Video for a hospital?

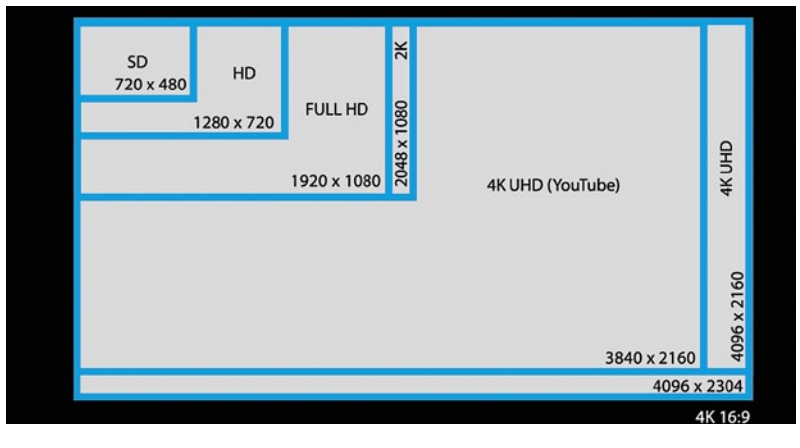
4K Video offers a higher resolution. Therefore, the amount of data is much higher. Small details are more visible on the image. Additionally, the workflow is different. Due to the higher resolution, cropping and zooming is no longer an issue. The result is a possible higher distance between camera or endoscope to the working area, which gives more space for instruments, especially during minimally invasive interventions.

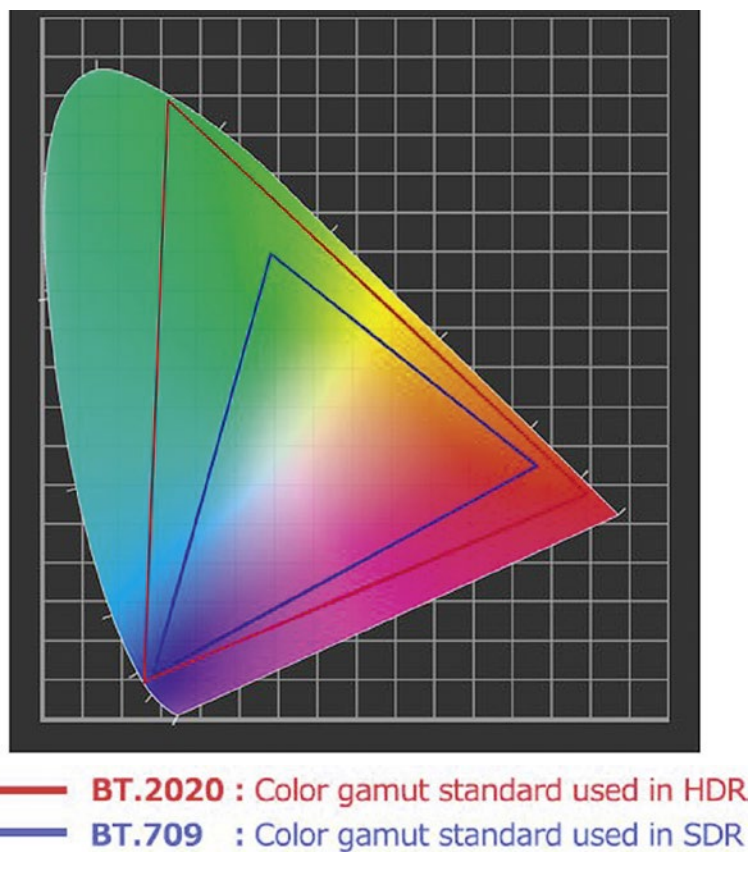
In addition to enrichment in the resolution, most 4k devices now start to support BT-2020 colour space. BT-2020 or REC2020 offer a much higher colour range, covering more of the visible human colours. Rein Medical offers a wider range of 4K video supporting products. The hardware products range from displays (Clinio and Silenio), to wall-integrated monitors and workstations. The sizes vary from 24 inch up to 55 inch. This IT manufacturer's product portfolio also includes a 75-inch wall-mounted monitor for large operating theatres, with a 4K display and UHD Quadview, on which up to four images are displayed simultaneously in Full-HD.

'All of these purely medical products guarantee ideal hygiene standards and offer high performance in addition to the IP protection,' the company confirms.

Smart OR and 4k: In an operating theatre, routing information to the right place or screen is vital. For this the company has developed Smart OR. This handles all routing tasks and also applies to the latest 4K Video technology. All the system's routing components support this already. 'It is a future proof solution no matter if you upgrade to 4k later on,' the manufacturer points out.

The new, smart OR hardware eco system offers compatible video transmitters and receivers. Those convert video and other signals to fibre-optic and back, which enables connection of various devices to one simple fibre-optical plug in a surgical room, enabling a flexible workflow. The boxes, Rein Medical adds, are fully IP protected and fulfil the highest hygienic standards.





The Alzheimer's Association International Conference

Exciting findings: 'flu vaccines and P-tau217

Adina Zeki Al Hazzouri PhD

Albert Amran

Elisabeth Thijssen

Professor Oskar Hansson

Suzanne Schindler MD, PhD

Svetlana Ukraintseva PhD

Report: Cynthia E. Keen

More than 32,000 people from over 160 countries registered for The Alzheimer's Association International Conference (AAIC 2020) in July. This largest and most influential international conference on dementia science had to be held virtually this year, when important highlights were aired.

P-tau217: An accurate indicator of Alzheimer's in laboratory blood tests

The ability to identify individuals at high risk of developing Alzheimer's Disease (AD), or at early onset, with simple, inexpensive blood tests would greatly aid research to develop therapeutic drugs to treat and potentially prevent the disease. Early detection with such tests could also facilitate immediate treatment to help slow brain damage and would help patients and their families to prepare for the future.

Advances in blood tests to identify abnormal versions of the tau protein identified in AD patients were presented at the event. The studies' results hopefully will accelerate clinical trials of AD biomarker blood tests.

Changes in the normal amount of tau and amyloid brain proteins create clumps in the brain known as plaques and tangles, and build-up of tau tangles is believed to correlate closely with cognitive decline.

Positron-emission tomography (PET) scans and cerebrospinal fluid (CSF) biomarker measurements are the current methods to identify changes in the brain when Alzheimer's is suspected before the dementia symptoms of AD appear. But these methods are invasive, very expensive, and not readily available.

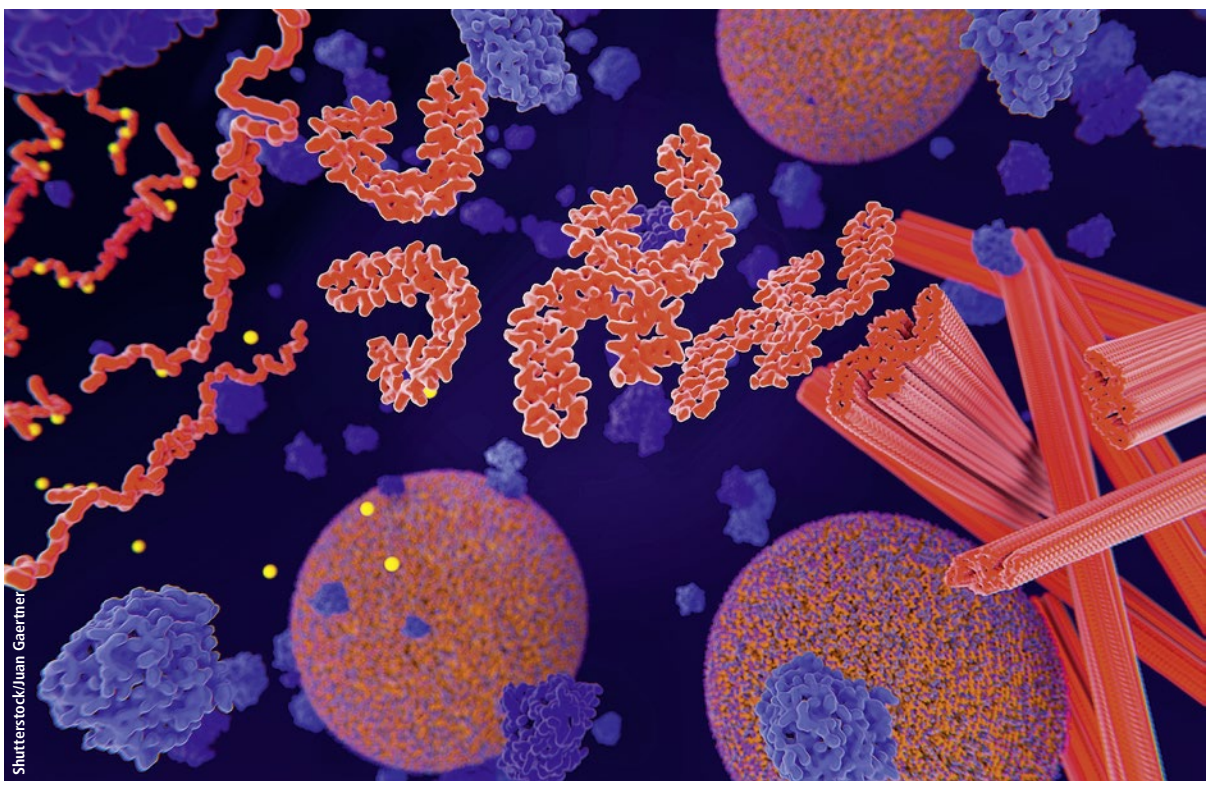
A multinational team of researchers, led by Professor Oskar Hansson MD PhD, of Lund University's Clinical Memory Research Unit in Malmö, Sweden, identified that the blood/plasma levels of P-tau217 could distinguish AD from other neurodegenerative disorders with a diagnostic accuracy of 89%-98% in a diversified three-study cohort of 1,402 individuals from Sweden, Columbia, and the USA.

P-tau217 is a form of tau found in tangles and also seems to correlate closely with the build-up of amyloid. The researchers discovered that P-tau217 was more accurate than three other current experimental biomarkers and comparable to PET imaging and cerebrospinal fluid biomarkers. It also was able to identify AD in post-mortem brain samples of patients with neurodegenerative disease with an 89% accuracy. P-tau217 levels were increased about sevenfold in Alzheimer's and started to increase 20 years before onset of cognitive impairment in individuals with a gene causing Alzheimer's, Professor Hansson reported. 'This test,' he said, 'once verified and confirmed, opens the possibility of early diagnosis of Alzheimer's before the dementia stage, which is very important for clinical trials evaluating novel therapies that might stop or slow down the disease process.'

Another factor of interest was that the test could distinguish individuals who carried a gene mutation leading to genetic early-onset Alzheimer's starting in middle age, as young as age 25. The study included 600 members of an extended family of 6,000 living in Columbia who carry the mutation.

Study findings from the Washington University School of Medicine in St. Louis, Missouri, and the Memory and Aging Center of the UCSF Weill Institute for Neurosciences in San Francisco, also supported the promise of plasma P-tau217 as a biomarker to identify AD in blood tests.

Neurologist Suzanne Schindler MD PhD, and colleagues from Washington University, used mass spectrometry to map the levels of both P-tau217 and P-tau181, high levels of which occur in the brains of AD patients. They determined that P-tau217 was more closely linked to the build-up of amyloid plaques in the brain as measured by PET imaging. Based on these findings, the researchers have launched an 1,100-participant clinical trial to develop and validate AD blood biomarkers.



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Alzheimer's disease: Tau proteins aggregate to neurofibrillary tangles in a neuron axon. The transport of synaptic vesicles is disrupted. 3d rendering.

Elisabeth Thijssen presented study findings from the UCSF Memory and Aging Center that showed both P-tau217 and P-tau181 are elevated in blood tests of AD patients, with a diagnostic accuracy of 96% and 91% respectively compared to PET imaging. The 617-participant cohort in their study included healthy controls as well as patients with AD and frontotemporal lobar degeneration (FTLD) spectrum. Results also showed that P-tau217 was five-fold greater and P-tau181 four-fold greater in AD patients compared to healthy controls and FTLD patients respectively.

Seasonal flu and pneumonia vaccinations reduce AD risk

Researchers from the University of Texas Health Science Center in Houston reported that a retrospective study of over 9,000 individuals under the age of 60 had a lower risk of developing AD if they received one flu vaccination, and that the risk continued to decline if they received subsequent annual vaccinations.

People who received at least one flu vaccination were 17% less likely to develop AD over the course of their lifetime. Multiple annual vaccinations reduced the risk by another 13%, according to presenter Albert Amran of the McGovern Medical School. He also reported that individuals who received their first vaccination at younger ages were associated with even greater decreases in risk.

The researchers developed their cohort from Cerner Health Facts, a database of electronic health records from over 600 participating hospitals and clinics hosted by UT's School of Biomedical Informatics. They used machine learning to analyse more than 310,000 health records to study the relationship between 'flu vaccination and AD.

'One of our theories of how the 'flu vaccine may work is that some of the proteins in the 'flu virus may train the body's immune response to better protect against AD,' Amran said. 'Providing people with a flu vaccine may be a safe way to introduce those proteins that could help prepare the body to fight off the disease.'

Similarly, individuals aged 65-75 who had a pneumococcal vaccination had a reduced risk of developing AD by 25% to 30%, according to a research study conducted at the Duke University Social Science Research Institute's Biodemography of Aging Research Unit in Durham, NC. The study included over 5,000 individuals participating in the Cardiovascular Health Study, a population-based longitudinal study of coronary heart disease and stroke in adults 65 years and older.

Svetlana Ukraintseva PhD reported that the research team studied associations between the pneumococcal vaccine, with and without an accompanying 'flu shot, after adjusting for sex, race, birth cohort, education, smoking, and the number of rs2075650 G alleles in the TOMM40 gene, a known genetic risk factor for Alzheimer's. They did not identify any additional risk reductions in individuals who also had a flu shot in this study cohort, but they did determine that individuals who were not carriers of the gene had the largest risk reduction of up to 40% when they had an anti-pneumonia vaccine.

Young adult obesity increases risk of late-life dementia

Mid-life obesity is a well-established-risk factor for dementia, but in what may be the first study of young adults aged 20 to 49, researchers from Columbia University's Population Research Center in New York City, have associated large body mass index (BMI) with higher late-life dementia risk.

Led by Adina Zeki Al Hazzouri PhD, a research team studied over 5,100 older adults, estimating their BMI starting at age 20. She reported that dementia risk was 1.8 times higher among women who were overweight and 2.5 times higher among obese women compared to women with normal BMI in early adulthood. Contrary to prior published studies, they found no association between midlife BMI and dementia risk among women.

Dementia risk for men, who represented 44% of the study cohort, was 2.5 times higher for those who were obese in early adulthood, 2.0 times higher for mid-life obesity, and 1.5 times higher for men who were overweight in mid-life. Interestingly, the researchers discovered that obesity in late life for both men and women decreased dementia risk, suggesting that high late life BMI may be protective.