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CRISPR-based test gives GPs quick results

Recent research in Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR) has identified two enzymes that can detect Covid-19 RNA as simply as a pregnancy test Jesús Pla, an eminent microbiologist at the Complutense University in Madrid, explained in an exclusive interview with European Hospital correspondent Mélisande Rouger.

Dr Jesús Pla MD PhD, teaches microbiology in the Department of Microbiology and Parasitology, Faculty of Pharmacy at Complutense University in Madrid. He coordinated the PhD Program in Microbiology and Parasitology between 2014 and 2019, and served as editor of microbiology journals and as evaluator of local, national and international projects, and for several scientific journals. Pla's recent work has focused on different aspects of the biology of the pathogenic fungus Candida albicans, especially the development of genetic tools in this fungus.

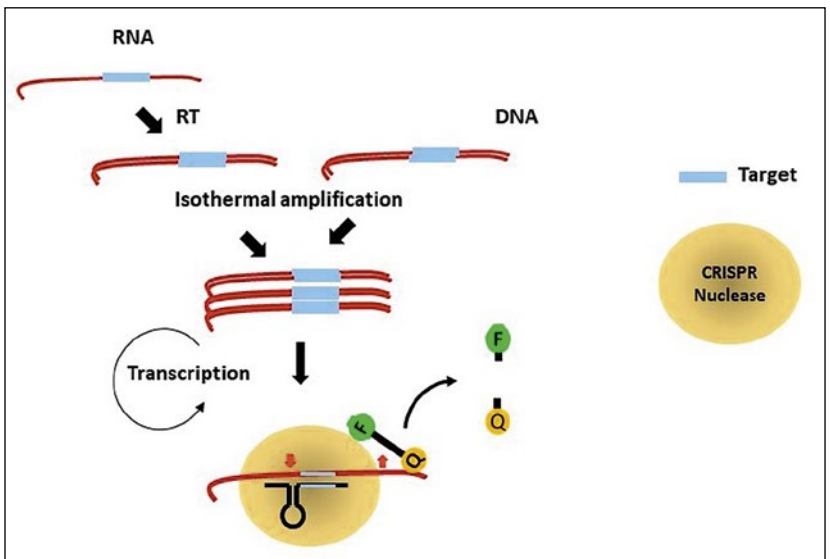
CRISPR technology could help alleviate workloads in packed hospitals and expand testing to primary care and lower income settings. The system provides a simple, rapid and reliable way to detect Covid-19, according to Jesús Pla.

Cas12 and Cas13 enzymes have been shown, upon recognition of the region of interest, to prompt what is called a collateral effect that acts on any DNA or RNA molecule present. 'Once you introduce a substrate in your solution and obtain fluorescence, you can cut not only what the enzymes recognise, but also every piece of DNA or RNA in the solution,' Pla explained. 'The triggered collateral activity, which degrades every piece of DNA or RNA around, can reveal the presence of Covid-19 RNA.'

Significant benefits

Labs don't even need a fluorometer to detect the virus's RNA in the solution; they can use a simple colour strip instead. 'It's not sophisticated, you won't get the precision and sensitivity you'd obtain with a fluorometer, but you will detect the virus's RNA. It's a visual test.'

Results can be obtained much faster with CRISPR-based tests than with PCR tests. 'PCR takes three to four hours, but you need to collect many samples, send them to a specialised lab, pass through a filer, run together, so in the end you have to wait one or two days minimum to get the result,' Pla said. 'With CRISPR-based tests, you get the results in an hour and a half.'



CRISPR technology enables the detection of either RNA or DNA-nucleic acid virus in clinical samples. The sample (i.e. nasal swab) is treated with a reagent's cocktail mix (Cas-mix) which consists of enzymes and other reagents that enable extraction and amplification of viral nucleic acid at a constant temperature in a single tube. Some protocols may use an additional transcription step. The key enzymes are either Cas12a (DETECTR method) or Cas13a (SHERLOCK method) nucleases that can recognise the viral nucleic acid (DNA or RNA) due to the presence of a specifically designed guide (black loop in the figure) that targets a region of the virus (blue line) (i.e., N, E genes in SARS-CoV-2). Upon this specific recognition, the nuclease triggers a non-specific collateral nuclease activity that acts on a quenched fluorochrome (F, fluorochrome; Q, quencher) present in the preparation mix, thus releasing a fluorochrome (F) which can be easily detected via fluorescence measures. Lateral flow assays for visual read outs are also available, thus simplifying the analyses. The system is scalable for high-throughput analyses. Several improvements and technical details have been omitted for simplicity.

This speed of execution could help alleviate workflow in strained hospitals, especially in cities like Madrid, where incidence recently broke the 700 per 100,000 infected cases, far above the WHO threshold.

The test's simplicity and low cost make it available to any lab around the world. 'It's very simple to do and detailed protocols have already been published,' Pla said. 'You need minimum experience in purifying enzymes, so any mid experience lab with a minimal knowledge of biochemistry can do the test. And that's the most expensive, the rest are just buffers, regions, substrates for detection, etc.'

Unlike PCR, CRISPR enables DNA amplification without having to use costly, sizeable equipment, such as a thermo cycler that ups and downs the temperature. 'With CRISPR,' he said, 'you can work at constant temperature, so anywhere works. You don't even need electricity, which could be a plus in developing countries. You could use it in any point of care.'

Two systems have been developed that showed sensitivity and sensibility in the 97-98% range and will be commercialised soon, Pla believes.

More tools to support PCR

Further tests are being developed that can help complement PCR, for example antigen detection, which helps detect the virus by identifying its protein. The more tests being performed, the better. 'If you could do a test every week in every population, Covid-19 would disappear. The problem is that you can't do PCR to 45 million people (Spain's population) every week,' he pointed out. 'You need to rely on quick methods and POC in order not to overload hospitals.'

CRISPR and antigen detection are not yet as powerful as PCR, but they are low cost, specific, reliable, simple, rapid and almost as sensitive. They can be performed in any point of care anywhere around the world. 'People with basic training and preparation could make an early diagnosis and take immediate decisions.

'The good point with CRISPR or antigen testing is that you can do it in primary care, directly at the GPs. You can get the results within an hour. The more tests we do, the more we control the disease,' Pla concluded.

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AI in clinical practice

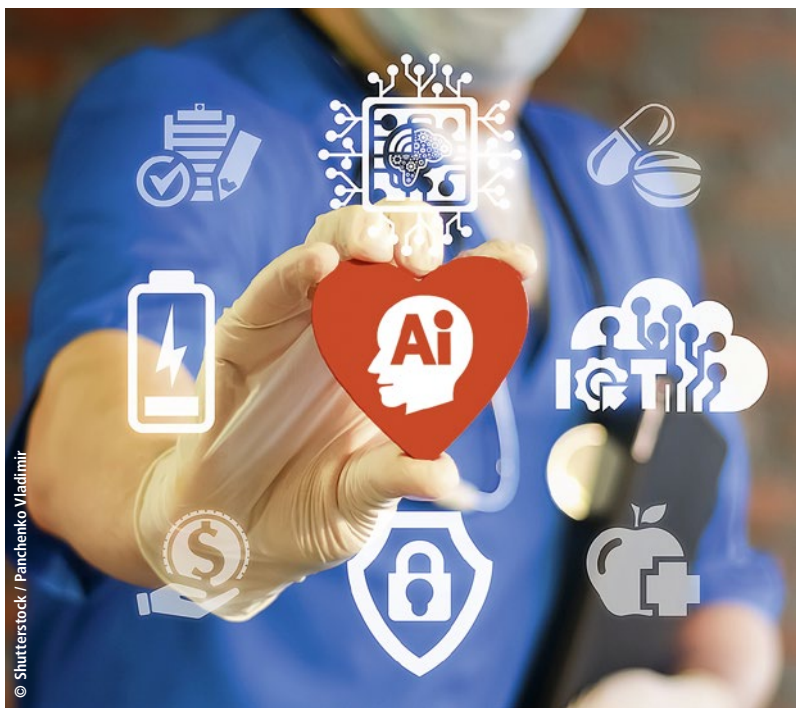
Hospitals must think big, small and new

AI in healthcare has been a trending, sometimes head-spinning topic for a few years – and, with the Covid-19 pandemic, clinicians have been presented with a whole new range of AI products that may or may not meet their needs. When it comes to choosing one's own set of tools, which criteria should prevail? A panel of European and US experts gave concrete examples of AI's current implementation in clinical practise and shared tips on how to start working with AI from scratch during the online Healthcare Information and Management Systems Society (HIMSS) Conference.

Report: Mélisande Rouger

Diagnosis and triage have become two of the most interesting indications for AI deployment in clinical practice, according to a recent initiative by the NHSX, a joint unit from National Health Service (NHS) England and the Department of Health and Social Care. The organisation launched the AI in Health and Care Award (AI award) to support solutions addressing the strategic aims of the NHS across the whole development pathway, by funding AI tools with over £50 million to kick-start their deployment into the real word and research.

With an overwhelmingly positive response, the first selection of submitted projects spans a wide scope of applications, such as breast cancer screening and emergency stroke assessment, according to Indra Joshi, Director of AI for NHSX. 'About 500 people applied and we selected 42 projects, ranging from image recognition that help recognise pathology, to how to triage images. In the UK, we're experiencing a huge rise in the production of images that need triage, in the acute setting as well as in routine care. We've selected tools for triaging appointments, to help clinicians understand when to move patients to different wards in the hospital.'



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The importance of thinking small

When talking about AI, people usually think big. AI's ability to diagnose or treat is an important role, and much tackled by developers. But, one should also include 'little AI' in the equation. Utility functions such as voice recognition are often disregarded, but are widely used in clinical practice, and they deserve much more attention, Christopher Ross, Chief Information Officer for Mayo Clinic in Rochester, USA, explained. 'One thing that's unheralded is those small places where AI is being employed and helps make a difference – things like computer assisted coding, annotation and enrichment of text, so that we can enrich data to make it meaningful signals that can be used by others.'

Regarding AI for diagnosis, Ross's team has developed algorithms to estimate kidney volume, an information obtained from radiological images that is used for a variety of therapeutic purposes. The Mayo Clinic has also published work on surveillance of patient populations for purposes of palliative care – notably to identify patients who are in decline or distress, and engage palliative care sooner and better.

The clinic's work on AI near the bedside includes identifying atrial fibrillation by looking at an ECG when a patient is not experiencing an event. 'It's been tricky to identify people with rhythm problems if you're not looking at them when they're having that problem,' he pointed out. 'The ability to look at a normal ECG and predict from that whether someone has a rhythm problem is very promising.'

In total, the Mayo is using or developing about 200 AI products from discovery to bedside, in various disciplines including radiology, neurology, cardiology, gastroenterology.

Starting AI from scratch

Not every organisation has such capacities as the Mayo or NHS. Developing one's own solutions is not a prerequisite for all institutions though. When thinking about AI, clinicians should rather look at a very important criterion: novelty. 'We're always looking at new technologies and don't use only things we develop ourselves.' Ross said.

For organisations more stretched for resources, a reasonable place to start is to determine which AI they can use. There might be areas where a simple "little AI" tool is all that's needed. Not every organisation needs to develop machine learning. It's all about using the right tool for the right problem,' Ross observed.

Healthcare systems that want to start using AI should draw road maps to describe how to adopt technologies to prepare adequately, he advised.

The recent Covid-19 crisis has put a magnifying glass on how to implement AI in a low resource setting, Joshi explained. 'At the peak of the epidemic, a number of companies came to sell their solutions,' she said.

Christopher Ross is Chief Information Officer for Mayo Clinic. He has has 32 years prior experience in healthcare, technology, and government. He is also Chair of HIMSS North America Board of Directors, and serves on the board of directors of Zipnosis, an emerging telehealth vendor. He was a member of the Health IT Standards Committee for the U.S. Department of Human Services from 2009-2016 and former chair of the board of the eHealth Initiative. He has a Bachelor of Science degree in economics from the University of Minnesota and MBA degree from the Yale School of Management. His areas of interest are digitization of medicine, artificial intelligence, patient empowerment.

Cardiac troponin I concentration measured at POC

Triage aided by a quick sensitive test

Large proportions of patients can be safely triaged either to rule out discharge or rule in lifesaving management – if following the European Society of Cardiology (ESC) Guidelines Class I recommendation of two serial measurements of hs-cTnI on admission and after one hour, if there are assay specific cut off values for the 0/1 algorithms. The Pathfast hs-cTNI assay is an approved system to determine highly sensitive troponin I recommended in the ESC Guidelines 2020, within the quick 0/1 hour rule out diagnostic algorithm. The manufacturer, LSI Medience Corporation, reports:

Pathfast hs-cTnI is a sensitive Chemiluminescent Enzyme Immunoassay (CLEIA) for the quantitative measurement of cardiac troponin I (cTnI) concentration in whole blood or plasma at the point-of-care (POC). The Pathfast assays are designed for Near Patient Testing (NPT) and can be used as an aid in the diagnosis of acute coronary syndromes (ACS) and in the risk stratification of patients presenting with suspected acute coronary syndromes such as chest pain in a hospital. Reagents are single use in all-in-one cartridges and up to six tests in parallel can be tested in one run. Besides highly sensitive troponin I, additional biomarkers as NT-pro BNP, D-Dimer, Myoglobin, CK-MB mass, hs-CRP and the new innovated emergency sepsis marker Presepsin can be measured at the same time with superior quality.

In less than 17 minutes the Pathfast system provides highly accurate, precise test results out of whole blood, plasma and serum similar to central laboratory analyser.

In clinical studies, Pathfast hs-cTnI assay has been evaluated for a 99th percentile upper reference limit of 29.0 ng/L at an imprecision of 6.1%, which fits the criteria of hs-cTnI assays recommended by IFCC and ESC. Moreover, gender specific cut off values were established and a 0/1 hour Rule-out and Rule-in algorithms of NSTEMI patients were evaluated. Recommended by the 2015 and 2020 ESC guidelines cTnI concentration were measured from 1,221 patients with suspicion of NSTEMI (669 for derivation and 610 for validation) using the Pathfast hs-cTnI assay in EDTA plasma samples obtained at 0 hour and one hour after admission of patients to the chest pain unit (CPU). As presented in recent publication, the identified cut offs for 0 hour rule-out showed 100% and for 0/1 hour rule out 99.7% negative predictive value (NPV). For 0/1hour rule-in 80.1% positive predictive value (PPV) were

Assay specific cut-off levels in ng/l within the 0 h/1 h

0 h/1 h algorithm	Very low	Low	No 1hΔ	High	1hΔ
hs-cTn I (PATHFAST; LSI Medience)	<3	<4	<3	≥90	≥20
hs-cTn T (Elecsys; Roche)	<5	<12	<3	≥52	≥5
hs-cTn I (Architect; Abbott)	<4	<5	<2	≥64	≥6
hs-cTn I (Centaur; Siemens)	<3	<6	<3	≥120	≥12
....					

Dr Indra Joshi is the Director of AI for NHSX, leading on the creation of the NHS AI Lab. Her other responsibilities include overseeing digital health initiatives within the NHS with a focus on data, digital health standards and evidence. Indra has a unique portfolio with experience stretching across policy, digital health, national project strategy and implementation; whilst remaining true to her professional training as an emergency medic. She is a Founding Member of One HealthTech – a network which campaigns for the need and importance of better inclusion of all backgrounds, skillsets and disciplines in health technology.

'Commissions from other countries asked if we could give some guidance, with questions on what criteria do we need to consider and where would AI fit in.'

Joshi insisted on remembering basic principles, for example the IT structure and how AI solutions would fit into an existing digital environment. 'If you're a digitally mature site and have a CIO, that's great. But you don't always do, and AI can be a totally foreign language. It's important to break it down into different messages you need to think about – have a list of what you need to think about when you don't know what you're looking for.'

The NHSX published a Buyer's Guide to AI in Health and Care, to help clinicians select the appropriate solution with regards to their environment (https://www.nhsx.nhs.uk/ai-lab/explore-all-resources/adopt-ai/a-buyers-guide-to-ai-in-health-and-care/).

shown. In total, more than 62% patients could be triaged successfully in this clinical study.

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The 5G wireless technology healthcare impact

HIMSS assesses potential values

In a virtual roundtable 5G discussion five healthcare IT experts, three senior executives from major USA medical centres and two consultants, discussed questions posed by members of the Healthcare Information and Management Systems Society (HIMSS).

Report: Cynthia E Keen

5G technology transmission speed is 10- to 100-fold quicker than third and fourth generation technology. It dramatically reduces latency, delay and response in data transmission from about 20 milliseconds on a 4G network to around 1-2 milliseconds – critical during interactive communications. In 2013, the European Commission (EC) established a Public-Private Partnership on 5G (5G PPP) to accelerate research and innovation in the technology and, in 2016, developed a European 5G Action Plan for Europe to launch 5G services in all EU member states by the end of 2020. As of June 2020, 12 member states, plus the UK, published national 5G roadmaps, according to the European 5G Observatory, supported by the EC to monitor 5G market developments.

USA telecommunications companies are launching various 5G initiatives. In 2019, Rush University Medical Center in Chicago became the first hospital system to deploy 5G, initially to replace its expensive, traditional, wired communications infrastructure with a wireless one. Saving: millions of dollars. With HIMSS vice president Stephen Wellman moderating, the roundtable, 'Removing Bandwidth Barriers: Impact of 5G in Healthcare', discussed how 5G could help providers during the coronavirus pandemic, the benefits of 5G for first responders, and whether 5G will inspire innovative new healthcare products.

The USA's commercial healthcare model has created costly and massive inefficiencies of treatment, especially for specialist or complex treatment; inequalities based on income and health insurance, and a geographic imbalance of medical resources, both well-trained practitioners and clinical specialists as well as medical equipment. The hope is that 5G can help change this.

Improving access

5G's ability to reach areas lacking healthcare and telecommunications services could expand them, said Callie Patel, Innovation Consulting Director at Healthbox, a HIMSS Solution and healthcare advisory firm. Telehealth, developed for rural areas in the '80s, is strongly supported by rural providers and 5G capabilities could, he believes, hugely boost those services.

'An individual in an area miles from a doctor's office, or hospital, is restricted to a phone call or smartphone face-to-face video encounter,' said Vishal A Jain, Vice President of Information Systems and Technology at the University of Maryland Medical System, Baltimore. 'If it's possible to run a lab test, and get cloud infrastructure and artificial intelligence (AI) involved to help with care, physicians may be able to safely, effectively deal with chronic or acute issues remotely.'

John Donohue, Vice President of Information Services Enterprise Services of Penn Medicine in Philadelphia, spoke of those travelling great distances several times to a healthcare facility before even seeing a specialist but, with 5G, they might have a remote consultation with a primary care physician and additional specialists before having in-person visits. Real-time telehealth could reduce 'red tape', expedite diagnosis and treatment, increase access to clinical experts, and lower costs.

Anshul Pande, Vice President and Chief Technology Officer of Stanford Children's Health in Stanford, California, said that small USA hospitals, facing bankruptcy or closure, could benefit from 5G because of its tools to connect instantly to large medical centres, to gain services such as immediate specialist consultations. Other applications: hospital-to-hospital services, e.g. consultations for emergency and surgical cases, and remote intensive care unit (ICU) monitoring and assistance.

Pande also said 5G telehealth would help in congested urban areas. Driving a few miles in San Francisco Bay can take hours. A 15-minute medical real-time interactive video consultation could avoid wasted time.

Michael Gibbons MD, CEO of digital health innovation company Greystone Group, and Chief Health Innovation Advisor to the Federal Communications Commission's Connect2Health Task Force, agreed. '5G will enable interactions with patients as if they were in a healthcare facility.'

In a 5G article in the Irish Journal of Medical Science (July 2020), Gerard Marshall Raj MD, of the Sri Venkateshwaraa Medical College in Puducherry, India, concurs that, by enabling a single provider to interact with multiple patients needing interventions, 5G could expand limited healthcare provider resources.

5G benefit to responders

In an emergency ambulance, 5G replacing 3G networks means A&E physicians can receive real-time health status data, and images instantaneously. 'A major challenge has been transmitting enough data to a hospital's emergency team,' said Pande. 'With 5G they could initiate treatment as soon as the patient arrives, or in the ambulance.' And, Donohue and Gibbons added, 5G could benefit a stroke patient living far from hospital, by receiving specialised drugs to counteract stroke damage quicker than the time taken to reach hospital. However, only knowledgeable physicians should order such dangerous and powerful drugs. Also, if emergency physicians provide real-time remote consultations, first responders might then provide on-site treatment or direct patients to an emergency care facility, rather than hospital. Jain said the University of Maryland Medical System is working with Baltimore city to do this, because hospital resources are strained by Covid-19. Telehealth consultations surged during the pandemic. Penn Medicine needed to set up physical telecommunications networks at remote testing sites. 'If a 5G network was available, this would not have been necessary,' Donohoe said. 5G availability could also enable remote monitoring of patients with exposure to Covid-19.

John Donohue is Vice President of Information Services Enterprise Services at Penn Medicine.

Anshul Pande is Vice President and CTO at Stanford Children's Health.

Other applications

These include robotic surgery, augmented and virtual reality applications to simulate surgery for physician training, and home care and remote patient monitoring, such as non-interventional blood sample analysis, seizure prediction, drug intake and dispensing. The HIMSS experts believe that, as 5G is deployed, the development of smart personal healthcare products and consumer apps will explode.

One year as a Senhance reference centre

Robotic system for surgeons and patients

In August 2019, the Evangelische Krankenhaus Wesel (EVK) was the first hospital in the Lower Rhine region in Germany to invest in a robotic system for abdominal surgery in one of its operating rooms (ORs).

In the beginning, the Senhance Surgical Robotic System, developed by Transenterix, was used for minimally invasive interventions in general surgery but today, its field of application has widened considerably. The EVK team is extremely happy with the new technology, says Managing Director Heino ten Brink: 'We'd make this decision again any time. For us, this type of OR support is the way forward and we are convinced that it will prevail.'

In addition to EVK, the operator Evangelisches Krankenhaus Wesel GmbH runs two community medical centres, three nursing homes, an out-patient nursing service and an out-patient palliative care service.

A fourth nursing home and a hospice are scheduled to be opened within the next three years.

The facilities cater primarily to patients in the region; two departments however have larger catchment areas: the neurology department, including a Stroke Unit and an early rehab centre, as well as visceral surgery, which is part of the oncology department. In the past two years the hospital invested heavily in digitisation: the HIS was updated and all employees were equipped with iPads to enable them to access clinical reports from anywhere. 'This digital support takes a huge load off our shoulders", says ten Brink and adds that "the Senhance system fits very well in our current strategy.'

In the beginning, the surgeons used the system only for less severe hernia and gall bladder interventions, but in the meantime they have gained sufficient experience and choose it for abdominal procedures such as diaphragmatic hernias, chronic reflux or intestinal conditions as well as in oncological tumour surgery. Gynaecology will be added in early 2021 when a new medical director will start his watch. Initially, the future head of department was sceptical about robotic surgery, ten Brink remembers, but after he had familiarised himself with the Senhance system he was excited and is now looking forward to the possibilities this new technology opens up.

The system provides the surgeon, who is comfortably seated patient-side at an open console, with detailed high resolution images in up to 6x magnification. The camera is equipped with an eye tracker, i.e. it is controlled by the surgeon's eye movements; the instruments inside the patient's body are controlled manually. An integrated tremor filter eliminates the minute – and natural – shivering movements of the human operator, thus enabling a degree of precision human hands would never be able to achieve. The advantages for the patients are obvious: smaller incisions, smaller scars, less pain – in total, a less stressful operation. In the meantime, the hospital's new technology has become the talk of the town – and the region. 'Many patients choose our facility because they have heard about our state-of-the-art equipment,' ten Brink said, adding: 'people are confident that they receive best possible care and specifically inquire about our Senhance system.' His initial fear the patients might be put off by the OR robot turned out to be unfounded: 'The patients' confidence in our hospital pays off.'

EVK Wesel is one of two reference centres for Senhance Robotic Systems in Germany and among 25 worldwide; in addition, interested surgeons and medical students are welcome to spend time at the hospital in order to gain a first-hand impression of the new technology – and their potential future employer. The current team, ten Brink reports, is proud to work in a facility that heavily invests in the future: 'For us, the robotic system is a USP in the region, which puts us ahead of the competition. In the longer term I'm sure this will translate into economic benefits.'

On 1 July 2020, **Heino ten Brink** began his role as Managing Director of Evangelisches Krankenhaus Wesel GmbH (EVK) when his predecessor Rainer Rabsahl took early retirement. Ten Brink, who studied business administration, had been deputy Managing Director at EVK Wesel since 2016. Before he joined EVK he was administrative director of Immanuel Hospital Bernau – Heart Centre Brandenburg and Head of Strategic Controlling, Business Development and a member of the administrative board at Evangelisches Krankenhaus in Mülheim an der Ruhr, Germany.

Please! No cables in our operating theatres

Refurbishment success in seven surgical units

Among refurbishments at seven operating theatres at Marien Hospital in Hamburg, Germany, are new PCs and wall-mounted monitors supplied by the Mönchengladbach-based medical IT manufacturer and developer of software and hardware Rein Medical GmbH. 'It was important to find a supplier which specialised in hardware for the operating theatre and who could supply high-quality products,' said Rolf Rathjen, Head of Medical Technology at the Marien Hospital in Hamburg. 'In addition, the PCs and monitors should integrate into the walls very well – we didn't want to see any cables in the operating theatre.'

Simultaneously, the hospital commissioned a different company to supply the OT integration software – not an unusual situation from Rein Medical's point of view. 'The special feature is the 4K UHD imaging: Our Operion three monitors are also available in UHD versions and are offered with various display diagonals,' explained Roland Schleberger, Key Account Manager at Rein Medical who was responsible for this undertaking. 'We are proud to have accomplished our first project with a 4K UHD display in Germany.' In all, Rein Medical supplied two 27" Operion displays with PC for wall installation and one 55" Operion display (4K) each for each operating theatre.

The company also provided a 24" Clinio PC with touch screen for the introduction. All monitors and PCs were installed on site by a team from Rein Medical, which is also responsible for training the Hamburg personnel. 'We could rely on our partner at all times in the project, Rathjen happily concluded. 'From our point of view, both coordination and delivery were perfect and always on schedule.'

Flawless live operation in under a year

Hamburg is highly satisfied with the progress. Since the end of 2019 the systems have run flawlessly in live operation in four completed theatres. 'Rein Medical has impressed us with the quality of the PCs and monitors, and also with the professional execution of the project,' Rathjen reiterated. 'The co-operation, also with the other service providers we commissioned, was uncomplicated and problem-free.'

Currently, phase three construction is underway at Marien Hospital, covering the refurbishment and prefabrication of the last three operating theatres, in which Rein Medical is also responsible for the IT equipment, analogous to the already renovated and newly equipped operating theatres. 'In future projects, too,' emphasised Rolf Rathjen, Head of Medical Technology. 'We will certainly be happy to return to the specialist knowledge and products of Rein Medical.'

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!

Live Stream Training and Conferences

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!

Monitor all Video Inputs!

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!

ATEM Mini ..... **265€***
ATEM Mini Pro ..... **535€***
ATEM Software Control ..... **Free**

Learn more at www.blackmagicdesign.com/nl

*Recommended retail price excludes VAT and shipping and delivery costs. Prices subject to change.
ATEM Mini for use in training, conferencing and teaching purposes only.

Blackmagicdesign

Perspectives on challenges to POCT use in acute care

Understanding sources of error

In an emergency, point-of-care-testing can provide results in minutes. However, sources of error must be understood to ensure result accuracy and confident diagnosis (particularly important during the current pandemic). Medical teams frequently use POCT devices to assess acutely ill patients; a hospital's diagnostic laboratory is responsible for the analysers, plus training non-laboratory staff in their use. To explain the challenges in POCT use from different perspectives, Dr Ulf Martin Schilling (Consultant in Emergency Medicine, University Hospital of Linköping, Sweden), Dr Andrei Tintu (Clinical Chemist/Laboratory Data Officer, Erasmus University Medical Centre, Rotterdam, the Netherlands) and Professor Suzanne Bench (Professor of Critical Care Nursing, London South Bank University and the Royal National Orthopaedic Hospital, United Kingdom) spoke at a workshop sponsored by the medical technology firm BD (Becton, Dickinson and Company) during the 23rd IFCC-EFLM European Congress of Clinical Chemistry and Laboratory Medicine.

A&E (Accident and Emergency) teams often deal with acutely-ill patients where the time to diagnosis and treatment can have a direct impact on their health and outcomes. If the patient is unconscious, the clinician has no ready means of obtaining a medical history or details of relevant events that led to hospitalisation. In this situation, the doctor would typically run through a list of obvious potential causes of clinical presentation. For example, are the patient's airways clear? Is breathing difficult? Is there a problem with circulation, as in a stroke or heart attack? Are there signs of trauma or seizure? If there are no obvious reasons for the patient's state, a more detailed investigation is necessary. According to Dr Martin Schilling, the reasons for a patient being unconscious are generally '70 percent metabolic and 30 percent structural', though the percentages vary with the patient's age, so analysis of patients' blood samples can help with early diagnosis and POCT typically gives results within a few minutes (a key advantage, compared to specimens tested in the laboratory).

Preanalytical variability is a key cause of poor diagnostic quality in the laboratory, shown to cause greater than 60 percent of all laboratory errors (Lippi G., et al. Preanalytical quality improvement: from dream to reality. Clinical Chemistry and Laboratory Medicine. 2011;49(7):1113–1126).

Likewise, preanalytical variability is also critical in POCT. For example, exposure of a blood gas sample to air can result in gaseous exchange between the air and sample. This may result in the measured values of the different gases not reflecting the patient's physiological levels. 'Sodium,' Schilling pointed out, 'may be diluted if a sample is taken from the same arm in which intravenous fluids were given' and, he reminded us, potassium levels are often elevated in haemolysed samples.

Inaccurate results can lead to misdiagnosis

In the stressful environments of an A&E and critical care units, there is the potential risk of misidentification of samples from different patients, leading to analysis of the wrong sample and resulting in the communication of erroneous values.

These types of preanalytical error which cause inaccurate results can lead to misdiagnosis and, critically, potentially incorrect treatment. POCT results can help to support different potential diagnoses and may indicate which laboratory tests or imaging techniques are warranted to make a definite diagnosis and start appropriate treatment. *But*, according to Schilling, this is helpful *only* if the POCT results are accurate, as he suggests 'we know that one in 20 results will be aberrant even by accreditation standards'.

Nurses in critical care often maintain a presence at the patient bedside, to provide physical and psychological care to the patient and support for relatives, whilst also managing complex equipment. According to Professor Suzanne Bench, this requires 'effective communication within the wider healthcare team, supervision of junior colleagues and maintenance of accurate documentation'.

Nurses are the biggest users

Studies show that nurses value POCT because it can 'help to speed-up decision-making and delivery' yet, Bench acknowledged, POCT can impact on nursing workload and time management. From focus group discussions with UK A&E and critical care nurses, Bench revealed that 'nurses are the biggest users of POCT in critical care' and nurses have a significant responsibility to clean and quality control the equipment, particularly out of hours and in smaller hospitals. Training in these operations is essential; if the equipment is not maintained properly, this can lead to inaccurate results.

Nurses report that training is necessary to ensure they understand the whole process, such as how to ensure that an accurate sample is obtained, why this is critical, and how to analyse the sample correctly. Nurses are also concerned about how POCT affects patient experience and health outcomes.

POCT blood specimen volumes are generally small (around one ml), but laboratory samples may be three ml or more. Because acutely-ill patients are monitored frequently, the volume of blood drawn may become significant, potentially leading to anaemia and, in extreme cases, requiring a blood transfusion. Preanalytical errors can exacerbate this problem, another reason why diagnostic sampling needs to be 'right first time'.

Frequent collections from patients also cause concern about infection control and patient comfort. Bench noted that 'the time taken for POCT also impacts on other aspects of care delivery and can lead to omissions in care provision for both the patient and the family'. For example, if the local POCT device is unavailable, a nurse may have to leave the patient and find an alternative instrument, possibly some distance away. The knock-on effect: the other nurses in the department may have to re-task to ensure coverage while their colleague is away. Therefore, having POCT systems that give reliable results are vital in critical care nursing.

Quality management

POCT devices are analytical instruments that fall within the domain of the hospital laboratory quality management, but are widely dispersed in many locations in different departments across a hospital. This creates a challenge for maintaining quality assurance and, in rare cases, the documentation of results for compliance purposes.

Generally, users of the POCT instruments are not experts in all aspects of the testing process but are medical professionals who use the instruments on an ad-hoc basis. Thus, the instruments need to be robust, fast and easy to use, and also deliver reliable results. Training clinical staff in the use of POCT instruments is a key laboratory role in many hospitals.

Dr Andrei Tintu used the example of the Erasmus University Medical Centre (4,500 POCT users) to indicate that the number of users needing training, together with the large number of POCT devices available, makes provision of the training difficult. This is an extra workload that the clinical laboratory is required to absorb. Tintu commented that, in theory, the easier a POCT instrument is to use, the simpler the training requirements should be. This may help to increase the operational efficiency and reduce costs of the clinical laboratory.

Clinical staff education

Tintu indicated that, given high staff numbers and turnover, there can be a challenge in maintaining accurate records for compliance purposes, to identify which staff are trained to use specific pieces of equipment. Educating staff on the POCT testing process and how preanalytical factors impact on sample quality, and hence the reliability of analytical results, is another vital laboratory responsibility. This helps to ensure early availability of results and fewer adverse patient events due to fewer blood re-collections.

Moreover, POCT instruments in a hospital must be verified for each sample type and test. By managing those devices, the laboratory quantifies the accuracy and reliability for the tests when conducted on these sample types, ensuring the staff obtains high quality results. The temptation for clinical users may be to test sample types which have not been verified by the laboratory's quality management system.

The reliability and accuracy of these tests will not have been determined, increasing the risk of aberrant diagnostic results, and the eventual possibility of patient harm.

To manage such use of non-validated tests, Tintu believes the best solution is robust communication between the laboratory and clinical teams. By the laboratory listening to the needs of POCT users, he believes further services could be provided to increase satisfaction among those users and ultimately improve patient care.

Clearly, different groups of healthcare professionals have differing views on what POCT should provide.

Dr Ulf Martin Schilling, Consultant in Emergency Medicine, University Hospital of Linköping, Sweden

Professor Suzanne Bench, Professor of Critical Care Nursing, London South Bank University and the Royal National Orthopaedic Hospital, United Kingdom

Dr Andrei Tintu, Clinical Chemist/Laboratory Data Officer, Erasmus University Medical Centre, Rotterdam, the Netherlands

What should or could POCT provide?

Blood collection devices and practices have evolved alongside the requirements of traditional diagnostic laboratory analytical instruments and, as such, are not optimised for use with POCT instruments, which are relatively new devices. Blood collection practices need to be designed and standardised to meet the different requirements of these devices.

This would help to eliminate the non-standard practical methods that healthcare professionals have adopted to provide workarounds for problems found in real clinical situations.

The current COVID-19 pandemic has reminded us that safety is also critical when considering POCT, with infection control impacting on patient and staff safety.

Managing acute cases increasingly depends on POCT devices maintained by healthcare science staff, operated by nurses (and others), and the results acted upon immediately by medical staff. However, despite good device maintenance and user training, sample quality and preanalytical errors can have an adverse effect on result accuracy.

* This opinion piece is based on the authors' presentations at the BD-sponsored workshop during the 23rd IFCC-EFLM European Congress of Clinical Chemistry and Laboratory Medicine. With many years' experience in sample collection BD is investigating how to decrease preanalytical issues, to improve care of acutely-ill patients and experiences of POCT users. The new POCT BD Veritor (TM) System also allows for the rapid detection of influenza A and B, Group A Strep, RSV and SARS-CoV-2 (CE approved).

The 4th Munich Point-of-Care Testing Symposium

The clinical potential of POCT

In 2019, the Central Laboratory of the Institute for Clinical Chemistry and Pathobiochemistry at the Klinikum rechts der Isar of the Technical University Munich, headed by Professor Peter B Luppa, organised the 4th of the internationally renowned Munich Point-of-Care Testing Symposiums. Dr Andreas Bietenbeck is senior physician at the Institute which for many years has been focusing on point-of-care diagnostics and initiated innovative research projects and developments. Our EH correspondent asked him about the clinical potential of POCT.

Interview: Walter Depner

EH: In recent years the capabilities of point-of-care testing have increased or improved considerably. Could progress be distinguished by three levels: clinical, technological and organisational – meaning integration into existing structures?

Indeed, this is one way to describe developments, even if the different levels cannot always be clearly separated. On the clinical level I find continuous monitoring particularly interesting, especially continuous glucose monitoring. It allows a much more precise identification of the time windows when the patient shows critical blood glucose levels. With this information the physician can counteract more effectively. Moreover, continuous monitoring is much more pleasant for the patient. Recently, I had the opportunity to test one of these continuous sensors.

After a very short time I had simply forgotten that I'm carrying the patch with the sensor. With regard to infections, POCT offers a further huge benefit because it allows quick identification of pathogens, no matter where you are, even in developing countries.

On the technological level we are seeing a continuous evolution of existing systems to make them ever more reliable. At the same time new types of POCT analyses are being developed, for example to detect circulating tumour DNA.

On the organisational level hospitals have recognised that they need special structures to be able to properly manage POCT. Thus, many facilities have established a POCT committee with a POCT coordinator.

While at Klinikum rechts der Isar sports medicine is not a focus, recently at a symposium on POCT in professional sports you talked about the possibilities new POCT offers in this particular field. Would you mind briefly summarising the ideas?

Sports medicine uses the fact that with POCT the transport of samples becomes obsolete and the test results are available much faster. Thus, POCT facilitates adjusting and optimising training on the spot. I cannot assess the individual results as I am not an expert in sports medicine.

These benefits are relevant not only in professional sports but in other areas as well. What trends are you observing?

Until recently, testing was limited to the clinical setting or particular applications such as professional sports, i.e. specialists. Today, monitoring is increasingly a part of everyday life. The new Apple Smartwatch, Apple Watch 6, is said to be able to

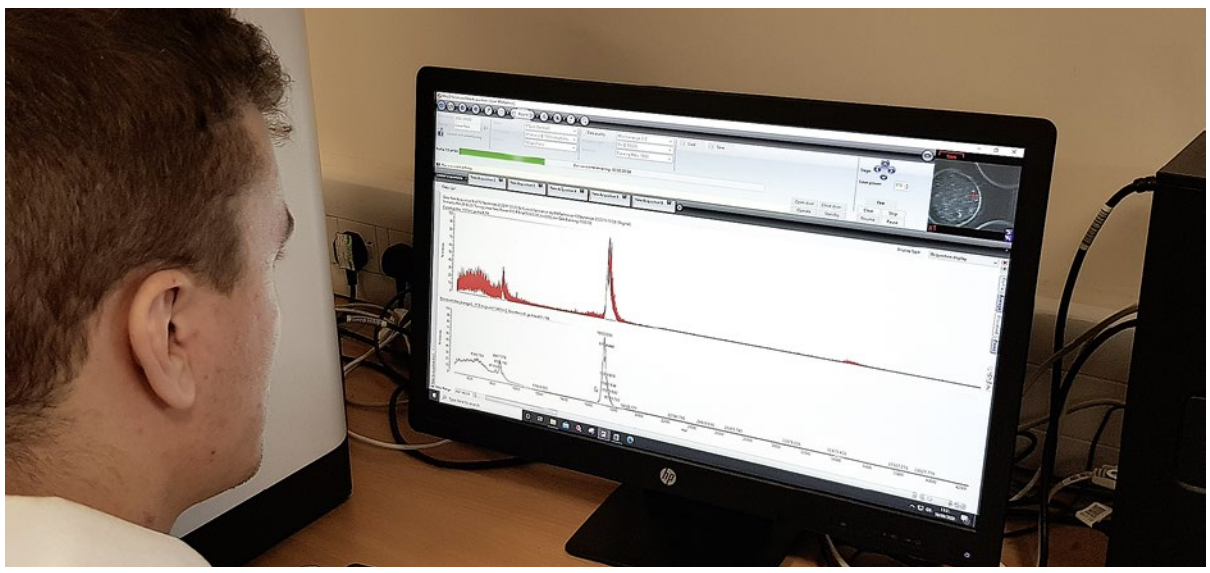
Continued on page 8

Andreas Bietenbeck completed his studies in 2012 with a doctoral thesis – magna cum laude – on biochemical methods in the lab. He received inter alia the INSTAND research award for projects on quality assurance in laboratory medicine and the Ivar Trautscholt award for junior scientists for his contribution to improve medical lab quality control. At the Institute for Clinical Chemistry and Pathobiochemistry, in the Klinikum rechts der Isar of the Technical University Munich, he researches quality assurance, medical informatics and POCT, on which he has co-edited several seminal publications.

Improve Covid-19 testing

Gargle and use mass spectrometry

A UK biotech laboratory has used mass spectrometry in a new approach to coronavirus testing. MAP Sciences developed a gargle test, which collects samples from the back of the throat, and avoids the unpleasant sensation of the current PCR (polymerase chain reaction) swab tests. From there, the sample is tested for coronavirus using mass spectrometry (MS) with high levels of accuracy.



With an under one hour turnaround, the developers believe the test is quicker, easier, cheaper and as accurate as current PCR testing and has the ability to pick up other viruses – as well as Covid-19 – such as H1N1 flu.

Professor Ray Iles, Chief Scientific Officer of MAP Sciences, based in Bedford, UK, says the test has been validated, with data now being gathered for regulatory approval, using samples from trials at Addenbrooke's Hospital in Cambridge and collaborators in the USA at Northern Illinois University.

The company seeks to take its gargle test to market and, as part of the UK's Covid-19 mass testing regime, to liaise with the country's government, which aims to ramp up testing capacity to 500,000 a day by the end of October.

Having spent many years working in the university sector, setting up biomedical and health science facilities and as a Dean at Colleges of Health, Iles set up MAP Sciences five years ago with the vision that MALDI-ToF could move from the research lab to being the 'go-to' clinical diagnostic tool. Underpinning this is the amount of information

Readout of the mass spec analysis on the computer

available from MS, an analytical technique that measures the mass-to-charge ratio of charged molecules or ions.

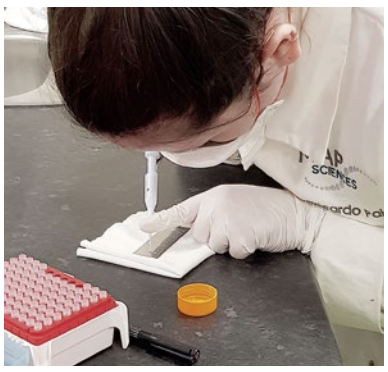
Ionising whole proteins without fragmenting

MALDI-ToF MS utilises an advanced method of protein pattern recognition – obtained from blood, urine or saliva - to diagnose various diseases and health disorders and rapidly deliver test results economically. In a typical MS procedure, a sample is ionised by bombarding it with electrons. But this breaks them into many small fragments. In MALDI, whole proteins are 'soft' ionised without fragmentation, and can then be analysed as single intact ions, creating simpler spectra within the mass spectrometer. This enables complex biofluids samples to be analysed and subjected to re-interrogation for further results. Professor Iles said cost and time taken for diagnostics remains a major hurdle in global healthcare, but MS screening offers a quick and cost-effective alternative for a range of tests. MAP Sciences had initially developed the technology with a view to screening populations for haemoglobinopathies and the most common genetic diseases, such as sickle cell disease or alpha or beta thalassemia from a pin-prick blood test.

The biotech firm developed these tests and proved their validity with colleagues at Addenbrooke's Hospital in Cambridge and Cambridge University, while also working with partners in the United Arab Emirates and the United States to confirm the technique works on their mass spectrometers.

Then the coronavirus pandemic struck. However, this unexpectedly presented a new opportunity. 'I always felt that the next step would be to use mass spectrometry and take samples and look for viruses, because viruses are packages of proteins,' Iles explained. From early March, MAP Sciences teamed up with Professor Jonathan Heeney at Cambridge University to understand the biology of the virus, and developed the biochemical approach for a new MS Covid-19 test.

Lab technician Vicky Lewis prepares the matrix plate for the mass spectrometer



The team specifically used the compact Shimadzu MALDI-ToF 8020 mass spectrometer to detect proteins associated with Covid-19 and created the new gargle test, which also overcomes the relatively unpleasant approach of PCR testing with swabs of the throat and up the nose.

How does the gargle test work?

'What we've developed,' Iles explained, 'is ways of enriching the virus in the sample, breaking the viral envelope, releasing these large glycoproteins and then identifying these glycoproteins on the mass spectrometer.'

Someone with suspected Covid-19 gargles with 10mls of water for 30 seconds and spits into a pot, which is then delivered to the lab where ice cold acetone is added to the solution to kill the virus and cause precipitation of large molecules. The sample is spun in the centrifuge with a chemical solution added to break up the virus and release the viral proteins, and then transformed into a small pellet and placed on a matrix plate. It's these viral proteins we look for to tell whether someone has Covid-19 or not, but it also means we can identify any other virus there as well – for example H1N1 flu.'

The matrix pellet is placed in the MALDI-ToF mass spectrometer. A readout on the computer screen produces peaks highlighting the presence – or absence – of the coronavirus, or any other virus. The mass spectrometer is looking for the SARS-CoV-2 Spike Glycoprotein-S1 Protein. 'We'll only get the S1 spike with virus being present,' explained Iles, who adds that the gargle test is a fraction of the cost of the PCR swab test for coronavirus and sampling can be performed at home and sent through the post to laboratories.

Professor Ray Iles is Chief Scientific Officer with the MAP Sciences Group, which develops medical and digital diagnostics (https://mapsciences.com/). His specific expertise lies in the assessment and measurement of biomarkers in biological fluids, with a passion for the finer details of clinical diagnostics and the instrumentation, and in developing new techniques. With a BSc in Bioanalysis, MSc in Immunology, and PhD in Molecular Pathology, he is a Fellow of the Royal Society of Chemistry, the Society for Biology and a Chartered Biologist and the founding Dean of Abu Dhabi University's College of Health Sciences.

Mass spec – compact size and flexible software

With data still being collated, Iles maintains that the gargle MS test is as accurate, if not more so, as the PCR test, believed to be about 80% accurate and with an unclear false positive rate. 'We are cheaper, we are faster and we are an alternative technique that can confirm or refute a PCR test. We also have quality controls in place and we are ready to go,' the professor confirmed.

Iles favours the Shimadzu MALDI-ToF 8020 because of its software flexibility and compact size. It can conduct about 500 tests a day, meaning significant investment in MS hardware will be required if the gargle test is to contribute to the UK government's testing aspirations, though Iles' team is working closely with Shimadzu over potential modifications.

Yet, he believes their sophisticated and affordable testing technology, with fewer consumables than other Covid-19 tests, will complement the simple binary Covid-19 tests currently in use and produce accurate results with fewer false positives as the global fight against coronavirus continues.

The clinical potential of POCT

Continued from page 7

measure heartbeat, ECG and blood oxygen. If these measurements are used for healthcare purposes, they have, for several reasons, to be treated with utmost caution.

Firstly, we don't know the quality of the measurements and we don't know which malfunction might happen. Moreover, if the user does not select properly, the results might show more healthy people than ill ones.

Operated by lay users even good quality testing equipment can show the monitored person as healthy, despite suspicious results.

Integration into existing structures encompasses the human aspects, i.e. organisational or responsibility aspects, and technical aspect, such as integration into existing LIS or HIS. Have those issues been solved, or are they solvable. Is this an ongoing problem?

Today the known problems can be solved. There are many stable options for a hospital to integrate POCT equipment in their LIS or HIS. If some of the stakeholders don't want such integration, problems arise – but they are non-technical. Today, however, we see new issues. Lab results, for example, are expected to be recorded – in addition to many other data – in the electronic patient file.

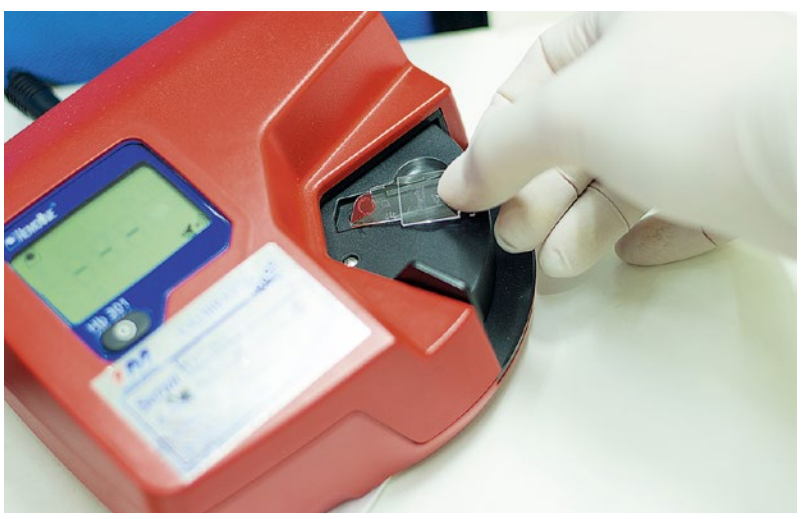
Particularly with POCT, it is difficult to record test results so that they can be interpreted correctly later on. For many tests, the POCT equipment shows considerable differences in quality.

Moreover, the reliability of the tests depends to a large extent on who performs the test: the patient, healthcare staff or a lab staff.

Success and failure are closely related to quality and thus responsibility. How, in your opinion, should these issues be settled?

In Germany we have a rather positive situation: we have guidelines for quality assurance of laboratory exams published by the national physicians' association, the so-called Rili-BÄK. These guidelines define minimum quality standards for POCT. Within this framework the individual facilities can decide on the organisational structure that best suits their needs.

One of the key aspects of POCT is the fact that, for it to be successful, different departments such as the wards, the lab and IT have to cooperate. Thus, a platform should be established where these stakeholders can regularly exchange ideas and experiences. In the end, however, there is one person who needs to be responsible, and it makes a lot of sense for this person to be an expert in laboratory analytics.



Addressing a broad range of research applications

Mass spectrometry advances

Since the Covid-19 epidemic took hold, the public has expected 'unprecedented progress from the scientific community,' observed Dan Shine, senior vice president and president of the analytical instruments division of Thermo Fisher Scientific Inc. 'A deeper analysis of proteins is critical to understanding disease, including novel viruses. New instruments, software and workflows can power discovery, improve productivity and enable breakthroughs across everything from small molecule studies to metaproteomics and biotherapeutics discovery.'

New on the market: Thermo Scientific Orbitrap Exploris 120 and 240 mass spectrometers

The role of high-performance mass spectrometry

The company has produced several new products built on its Orbitrap platform to help expand research applications for scientists working in proteomics, metabolomics, biopharmaceutical characterisation and small-molecules. The Thermo Scientific™ Orbitrap Exploris™ 240 mass spectrometer is among the new systems.

Daniela Zimmermann (EH) asked Deb Bhattacharyya PhD, Senior Manager at the Clinical and Forensic Toxicology division of Thermo Fisher Scientific, what kind of clinical lab would typically use what she called the "beginner model" Thermo Scientific Orbitrap Exploris 120 mass spectrometer, and asked him to explain the main difference between this and the Orbitrap Exploris 240 analytical software and intelligent algorithms.

'It might not be fair to call the Orbitrap Exploris 120 MS the "beginner model",' Bhattcharyya said. 'This instrument can work at a resolution of 120 K and, as we have shown via published data, the Orbitrap Exploris 120 has been used successfully to address an extensive range of clinical research applications – from small (testosterone, steroids, immunosuppressants) to large (IGF-1 intact analysis) molecules. The published application data highlighted the benefits of an optimal combination of high resolution, speed, robustness and sensitivity that the Orbitrap Exploris 120 can offer. Hence, for every clinical research laboratory focused on untargeted to targeted screening, and targeted quantitation – the Orbitrap Exploris 120 can become an extremely powerful instrument which, combined with Thermo Scientific Vanquish UHPLC can offer robust, reliable, reproducible LC-HRAM(MS) data for any analyte, regardless of the matrix complexity.'

Could creating an efficient pocket mass spec system needing less power be possible one day?

I learned, at a very young age, that it's never wise to say "never". While such an instrument does not exist today, when we consider the evolution that the world of mass spectrometry has experienced, mainly, in the last two decades – having a portable MS that can be moved around from one place to another might be possible. The quadrupoles and the Orbitrap has certain lengths. However, it is clear that the footprints of the Orbitrap Exploris series is significantly smaller relative to that of its predecessor (Q Exactive MS Series). It's fair to say that not only the Orbitrap Exploris is a benchtop high-resolution accurate mass (HRAM) spectrometer, but it actually is not too much larger than the typical triple quadrupole mass spectrometer that we manufacture.

Miniaturisation is the buzz word of the present world. Laboratory bench-space is getting smaller with every passing day. While there are on-going research studies to explore further miniaturisation of high-end analytical instruments, such as, mass spectrometers, it would be extremely important to ensure its quality of results, accuracy, reliability and reproducibility. Miniaturisation of the instrument, along with assured high-quality data, will surely make MS a very popular technique across both research and applied fields.

The Orbitrap family works with eight software packages. Where is Thermo Fisher Scientific heading with this?

Software is the medium (or conduit) that connects the user to the analytical instruments. As the importance of HRAM powered by Orbitrap technology gains momentum, the application areas that are looking at HRAM for research and routine use are also expanding fast.

While Orbitrap technology is the gold standard for Proteomics and other forms of Omics research, it is now regularly used across many other application areas ranging from clinical research to toxicology, from environmental to food safety, from small molecule Pharma to Biopharma applications. Each of these application areas require specific information, which is catered to by a certain software package – thereby explaining the need for a suite of software that works with our newly released Orbitrap Exploris Series MS.

Ongoing software developments are being made to address for the growing challenges faced by researchers as well as analytical scientists in applied market. The effort of our continuous engagement can be seen in the upgrades we make to our software packages – making them powerful, stronger and easier for every user, regardless of their expertise.'

Remote service

Would your ability to remotely offer preliminary service enable the process of individualised service offerings and also help form a guideline for the next generation of systems?

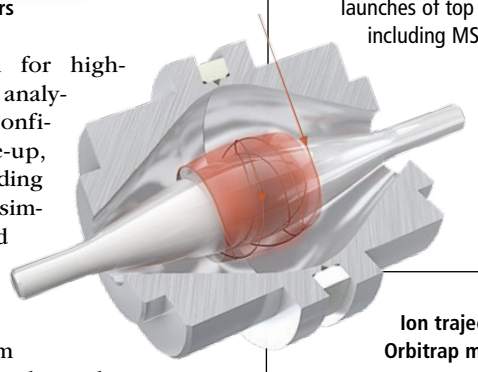
It's definitely a unique way for us to determine the specific requirements for MS users. In addition, the knowledge accumulated through our wide array of install bases helps us in ideation, development of next generation products where the commonly found issues are easily resolved. One such example in the newly released Orbitrap Exploris MS series is the Thermo Scientific™ EASY-IC™ calibrant ion source, which enables improved mass-to-charge ratio (m/z) assignment and delivers sub-ppm mass accuracy consistently without any user intervention for at least five days.

The integrated intelligence is obtained via a unified architecture and a common foundation ensuring what next generation systems deliver are easier to use, without sacrificing high performance. The web-based monitoring, data storage and information sharing helps in monitoring, evaluating and improving system utilisation for every user organisation.'

Current virtual exhibits

Due to Covid-19 restrictions, Thermo Fisher Scientific is providing online programming and virtual exhibits to introduce scientists to its new products that build on the Orbitrap platform and expand research applications.

The company explains that the Exploris 240 mass spectrometer expands the Orbitrap Exploris platform and is designed to give the analytical performance necessary in research for high-throughput analyses and confident scale-up, while providing operational simplicity and streamlining time-to-result.



Ion trajectories in an Orbitrap mass spectrometer

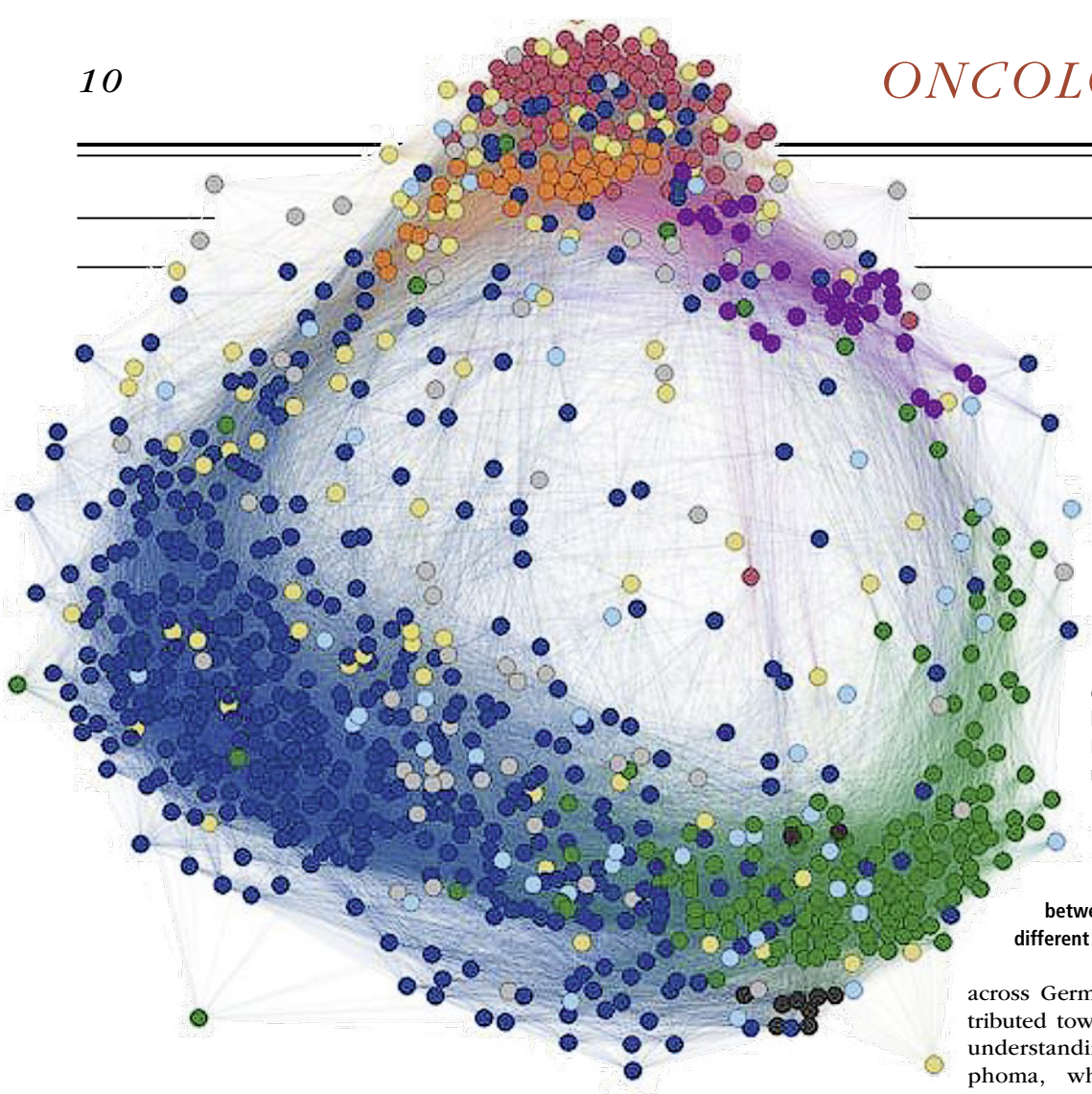
The firm also adds that the Orbitrap Exploris 120 MS 'delivers demonstrated qualitative and quantitative capabilities synonymous with Orbitrap high-res accurate-mass (HRAM) spectrometry, with internal calibration assuring consistent data quality and decision-making. The new instrument is designed to deliver proven measurement capabilities in a system developed for increased productivity.'

Thermo Scientific Proteome Discoverer 2.5 software 'provides high confidence during peptide identification, more accurate quantification and higher throughput data analysis for proteomics researchers,' the company adds. 'Deep learning-based prediction of tandem mass spectra, facilitated through a new collaboration with MSAID GmbH, a software company transforming proteomics through deep learning, allows more scientists to benefit from vast improvements in identification confidence and reproducibility.'

Deb Bhattacharyya gained his MSc in Chemistry from the Indian Institute of Technology (Mumbai, India) and a PhD in Chemistry from Emory University (Atlanta, GA, USA). He served as a Research Associate in the Biophysics and Biochemistry Department at the University of North Carolina – Chapel Hill, focusing on structural elucidation of Protein-DNA, Protein-Protein complexes leading to development of critical therapeutic pathways. he was also a visiting fellow at the University of Texas SouthWest Medical Center. At ThermoFisher Scientific, as Senior Mareting Manager for Clinical and Forensic toxicology business he focusing, Clinical Research, Toxicology, and Clinical Translational Research. Author-ship: over 50 peer reviewed articles. Plus led launches of top new technologies, including MS based solutions.

The massive Pan-Cancer Project

Cancer develo begins within



Visualisation of diversity of B-cell lymphoma. Each circle represents a tumour (patient), with the colours differentiating between the different types

Launched in 2011, the Pan-Cancer Project involved more than 1,300 scientists and clinicians in 37 countries, and analysed more than 2,600 genomes of 38 tumour types. Discovery: The first indications of cancer development can be found in genes at a very early stage, which triggers new opportunities for treatment. Within the project, Leipzig-based scientists specifically analysed the DNA material. Initially in our interview, Dr Hans Binder, Managing Director and research leader at the Interdisciplinary Centre for Bioinformatics (IZBI) at Leipzig University explained how the cancer cells examined.

Interview: Katrin Schreiter

'Doctors took tissue samples from patients and diagnosed the cancer. Pathologists examined the tissue to make further, detailed diagnoses and laboratory medics and molecular biologists extracted the DNA and sequenced it. The sequence data provided information about the mutations. We have developed bioinformatical methods and used them to derive mutations and further information such as activity of the genes and possible problems with biological functions from the sequence data. This makes it possible to differentiate between types of cancer through a comparison of the nucleotide sequences along the DNA, or respectively the frequency of RNA copies read out in samples from the cancer patients.' The findings: 'With our partners across Germany we contributed towards a better understanding of lymphoma, which mechanisms lead to its origin and development; why the affected cells degenerate… yes, this was a vast amount of data involving millions of sequence positions in around 20,000 genes, from hundreds to a few thousand patients respectively, which the bioinformaticians prepared in such a way that conclusions can be drawn.'

Can those conclusions be generalised?
Cancer is a complicated disease which develops because of defects in the genome. Strictly speaking, with each patient it is not a disease but actually a multitude of defects which can have different effects. For the first time, the project gave an overview of the possible defects.

Could these then be addressed with targeted treatments?
Unfortunately, a genetic defect cannot simply be repaired, as side effects of treatment are not predictable and controllable. This makes the disease so difficult. But research is progressing. It is important to learn how cancer works. We have already developed improved diagnosis- and treatment options, such as immunotherapy. Apart from fighting cancer we also need to adjust treatment in such a way that patients can live with the disease as best and for as long as possible.

Biophysicist **Hans Binder** has been Managing Director of the Interdisciplinary Centre for Bioinformatics at Leipzig University since its foundation in 2002. He leads the research group on 'Omics, bioinformatics for health and systems biology' at the IZBI. He focuses on transcriptome and genome data from sequence analyses to understand the molecular and systemic mechanisms of diseases, particularly cancer. His team develops bioinformatical procedures using machine learning, and is involved in several international and national research consortia.

Have you gained any insights on how cancer presents in the initial stage?
On a DNA level you mostly find so-called driver mutations. This often affects genes with key functions and leads, for instance, to increased cell division, i.e. the cells infiltrating healthy tissue. Some of these changes can be detected in the genes, decades before the disease manifests. But simple and standardised treatment is not possible: Mutations make the cancer very variable; it adapts and becomes hard to fight.

This sounds like a multitude of cell changes.
Yes, the variety is enormous. The important thing is knowing that each person's genome is unique – which is why every cancer, as a disease of the genome, is also unique. However, the variants can often be grouped to devise specific treatment rules.

Are these insights a further step towards personalised medicine?
Most definitely. It will be the responsibility of Cancer Research Centres (and already is in parts) to analyse the DNA of each patient to understand the specific characteristics of their disease and then tailor their treatment accordingly.

Detection during, not between screenings is best

Study delivers breast cancer advice

Tumours with the same biology have different prognoses based on their method of detection, and this information should be taken into account when deciding which treatments might be needed, a Dutch researcher explained at the 12th European Breast Cancer Conference.

Dr Josephine Lopes Cardozo is a PhD candidate at the Netherlands Cancer Institute in Amsterdam, and a medical fellow at the European Organisation for Research and Treatment of Cancer (EORTC) in Brussels, Belgium. Her lengthy interest in breast cancer continues with a focus on the role of the 70-gene signature for clinical decision-making in breast cancer, to evaluate how to select those patients who would benefit from adjuvant systemic therapies or not.

High-risk breast cancers detected in screening program mammograms have a better prognosis than those cancers detected in the interval between screening rounds, suggests an analysis of results from over eight years' follow-up of a major international clinical trial.

A team of Dutch researchers looked at cancers that had been identified as being high risk by the 70-gene signature test, but differed in the way they were detected, i.e. either during the biannual national screening program or in the two-year interval between screenings, typically when a lump or other abnormality is detected at the GPs and a mammography is prescribed.

The researchers compared the data of over 1,000 Dutch breast cancer patients aged 50-70 who had enrolled in a European phase III clinical trial and participated in the Dutch national biannual screening program.

The authors found that although some tumours may have the same genetic make-up, the way they are detected makes a significant difference to the period of time before the disease starts spreading or results in death – a lapse of time known as the distant metastasis-free interval (DMFI). 'We found a significant difference in survival between high-risk cancers detected during screening or in the interval between screenings.

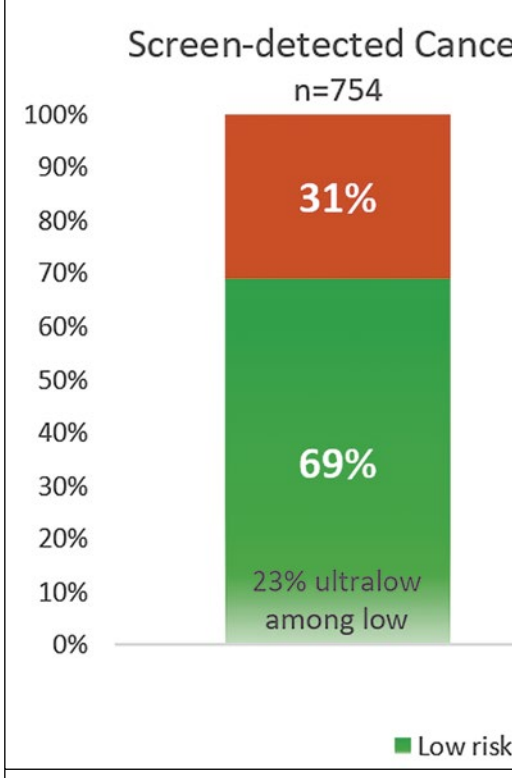
The eight-year DMFI rate was higher among women with screen-detected cancers than for women with interval cancers: 93.8% versus 85.2%,' said PhD candidate Dr Josephine Lopes Cardozo at the Netherlands Cancer Institute (NKI) in Amsterdam, and medical fellow at the European Organisation for Research and Treatment of Cancer (EORTC) in Brussels.

Additionally, those patients with high-risk tumours detected in the interval between screenings had a 2.4-fold increased chance of developing distant metastases compared to those whose cancer was detected during screening.

These findings complement previous research done by the same group showing that interval cancers more often have a high-risk genetic profile, as shown by the 70-gene signature, and are therefore at higher risk of distant metastases. 'We know these interval cancers are more aggressive and thus also have a worse prognosis,' Cardozo explained. 'However, there are also screen-detected cancers with a high-risk 70-gene signature.'

MINDACT

In their current work, Lopes Cardozo and colleagues looked at the data of 1,102 Dutch patients enrolled in the MINDACT study, a large prospective trial testing the 70-gene signature MammaPrint as guidance for adjuvant chemotherapy in breast cancer patients across nine European countries. The team calculated differences in DMFI for high, low and ultra-low risk tumours, as classified by the 70-gene signature, which



Different proportions of 70-gene signature results among screen-detected and interval cancers

pment the genes

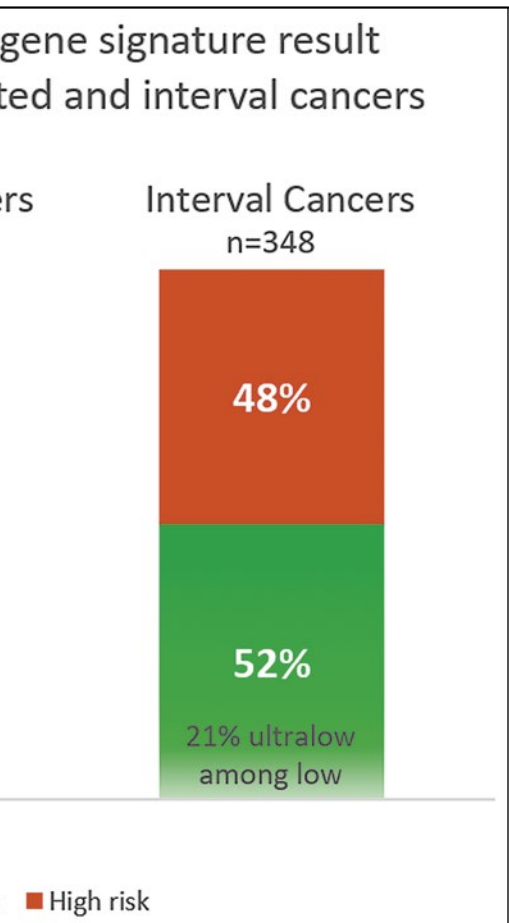
Will the CRISPR method become more important in this context?
CRISPR is a procedure used to precisely modify DNA building blocks in the genome. It works like genetic scissors. CRISPR is now of great importance for basic research, for instance to examine consequences of driver mutations in laboratory experiments. It's too early for its use in therapy because collateral damage is not predictable. But there are other ways of fighting cancer.

Cancer cells have the ability to adapt and hide. Therefore, the objective is to expose them to allow the body's immune system to fight them, hence intensive research in immunotherapy – with the first success: One strategy is to remove the "invisibility cloaks" from the cancer cells, allowing the immune system to recognise and destroy them. Another strategy is the removal of patients' immune cells to teach them to recognise cancer cells, then to inject these enhanced cells.'

The project has ended. What will follow now?
One of the objectives now is to implement the findings in clinical routine, to finetune diagnoses and circumvent resistance to treatment. A further project is aimed at understanding and avoiding the damaging side effects of immunotherapy. Molecular DNA analyses play a key role here.

THE PAN-CANCER PROJECT

The international research team examined 2,700 cancer genomes from different types of cancer in this meta-analysis. The group of scientists also includes researchers from Leipzig University: Dr. Hans Binder, Managing Director and research group leader at the Interdisciplinary Centre for Bioinformatics (IZBI), Professor Markus Loeffler, Director of the Institute for Medical Informatics, Statistics and Epidemiology (IMISE), and Professor Peter Stadler of the Institute for Informatics, Chair of Bioinformatics, and their teams.
They analysed sequence data of malignant lymphoma, i.e. cancer of the lymphatic system. This involved the detailed examination of DNA mutations, problems with DNA methylation and related changes in gene expression, i.e. gene activity. The Leipzig-based bioinformaticians contributed significantly to the understanding of the molecular causes of the disease and of its heterogeneity. They have been active in different areas of genome research of cancers for over a decade and are leaders in this field internationally. Work arising from the worldwide project will now be continued and centre around clinical implementations.



looks at the activity of 70 genes in the breast cancer tissue. 754 cases were detected during screening and 348 during the interval between screenings.

The data indicated that 50% of patients reached at least 8.6 years of follow-up and there were 83 occurrences of distant metastases or death due to breast cancer.

When looking at survival rates at eight years, researchers found that patients with screen-detected cancers had an eight-year DMFI rate of 98.2% in 118 women with ultra-low-risk tumours, 94.6% in the 398 women with low-risk tumours, and 93.8% in the 238 women with high-risk tumours.

Patients with interval cancers had an eight-year DMFI rate of 97.4% in the 39 women with ultra-low-risk tumours, 92.2% in the 143 women with low-risk tumours, and 85.2% in the 166 women with high-risk tumours.

Towards tailored treatments

These results suggest that the method of detection is an additional prognostic factor in patients with high-risk tumours, and that the combination with genetic information may help to tailor treatment better for these and other patients, Lopes Cardozo believes.

'The method of detection combined with the 70-gene signature can further optimise treatment for this group of patients who have a high risk of recurrence, the cancer researcher concludes, adding: 'For patients with a very low risk of recurrence, longer follow-up may also help to identify those who are currently at risk of being overtreated.' (MR)

Breast cancer risk study

More personalised screening needed

Women with incident and proliferative benign breast diseases (BBD) are likelier to develop breast cancer, a Spanish researcher explained during the 12th European Breast Cancer Conference in October. These findings support the idea of designing personalised breast cancer screening strategies to improve effectiveness.

Report: Mélisande Rouger

BBD, a group of non-cancerous breast disorders, have been proved to increase chances of subsequent breast cancer. New evidence has emerged that the time they are detected in a national screening programme indicates which lesions are likelier to become cancerous, according to a team at the Hospital del Mar Medical Research Institute in Barcelona.

'Our results show that women with a benign breast disease diagnosed from the second screening onwards have a significantly higher subsequent risk of breast cancer than those with a BBD diagnosed on their first mammographic screening,' said Dr Marta Román, a senior researcher in the epidemiology department at the Hospital del Mar Medical Research Institute, during the conference.

Proliferative BBD detected from 2nd screening onward linked with higher risk

BBD may be detected on the first occasion a woman attends breast screening, usually at age 50 in Spain, and are then classified as 'prevalent' BBD. Those BBD detected on subsequent visits, which occur every two years, are classified as 'incident' BBDs.

With their study, just published in The Breast (Differences in breast cancer risk after benign breast disease by type of screening diagnosis (https://doi.org/10.1016/j.breast.2020.09.005), Román and her colleagues assessed differences in the risk of breast cancer after diagnosis of BBD according to whether it was diagnosed in an incident or prevalent screen.

The researchers analysed data from 629,087 women who underwent 2,327,384 screening mammograms between 1995 and 2015, with follow-up until 2017, across seven centres in Catalonia, Asturias and Cantabria. They found that women diagnosed with incident BBD had a 2.67-fold increased chance of developing breast cancer than women with no BBD, while women with prevalent BBD had a 1.87-fold increased risk.

The authors also classified the BBDs as non-proliferative or proliferative, depending on whether or not the breast tissue showed an increase in the growth of certain cells, such as the ductal cells found in ductal hyperplasia, in which there is an overgrowth of cells lining the ducts inside the breast.

The team found that women with proliferative BBD had a 3.28-fold increased chance of breast cancer compared to women with no breast disease, while women with non-proliferative BBD had a 1.96-fold increased risk.

'We found the highest risk of breast cancer in women with incident, proliferative BBD. They had a nearly four-fold increased risk of breast cancer compared to women with no BBD,' Román said.

Women with an incident, non-proliferative BBD had a 2.39-fold increased chance of subsequently developing breast cancer compared to women with no BBD; women with prevalent, proliferative BBD had a 2.85-fold increased risk; and women with prevalent, non-proliferative BBD had a 1.63-fold increased risk, the study showed.

A call for personalised screening

The researchers hope that their findings will be useful in designing personalised breast cancer screening strategies to improve the effectiveness of breast cancer screening.

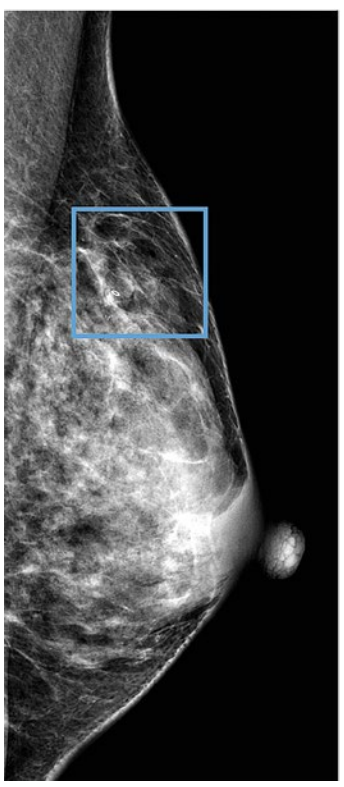
'The likelihood that a woman will benefit from screening mammography depends on her risk for developing clinically significant breast cancer in her lifetime. Taking individual risk factors beyond age into account should enable the classification of women into groups at varying risk of breast cancer,' said Román, whose group is part of MyPebs, an international randomised controlled EU funded trial to investigate whether a risk-based breast cancer screening strategy, based on a clinical risk score, is more effective than standard screening.

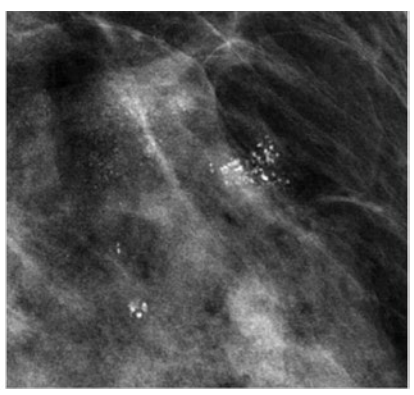
Personalised risk-based screening going beyond the current 'one-size fits all' recommendation may increase the effectiveness of breast cancer screening, she believes. 'Including information from BBD, in addition to other factors, to develop risk-based screening approaches can help with the prediction of whether a woman would develop breast cancer in a defined period.'

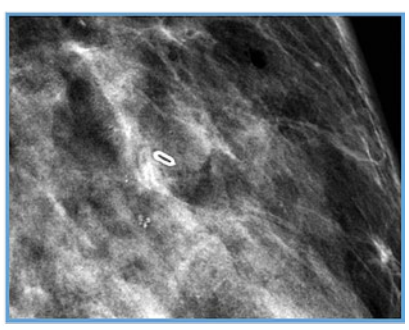
Modifying the screening interval, the method of screening - mammogram, ultrasound or MRI - or the age range in which the woman is invited for screening participation could all help improve detection, she suggested.

The new findings should be considered when discussing risk-based personalised screening strategies, to help clinicians understand the different risks associated with benign breast disease and improve the accuracy of breast cancer risk predictions.

'Society demands that breast cancer screening, as we know it today, changes and becomes more personalised, integrating all the information that is available,' Román concluded.

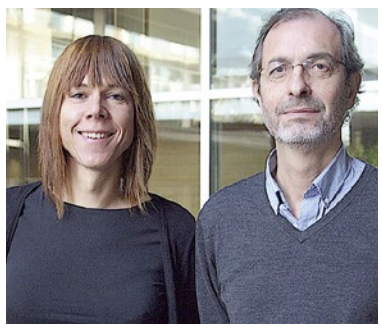






Benign breast disease as seen in a screening mammography.

Dr Marta Román is part of the research group in Epidemiology and Evaluation from Hospital del Mar Medical Research Institute (IMIM). She gained her PhD in Biostatistics at the Universitat de Lleida, and a Masters in Statistics and Operational Research from Universitat Politecnica de Catalunya. Román has extensive experience in epidemiological and clinical research facing national and international projects in the evaluation of breast cancer screening. She is the Director of a PhD thesis dedicated to investigating personalized breast cancer screening strategies. The researcher has published 39 peer review articles on breast cancer screening.



Marta Román and Xavier Castells, Head of Epidemiology at Hospital del Mar

Detected and defined: two distinct immunopathological profiles

Experts unlock Covid-19 secrets

Experts have identified two distinct immunological and cellular profiles in the lungs of Covid-19 patients which they believe could help define treatment pathways.

Report: Mark Nicholls

From some of the earliest Covid-19 autopsies conducted in Europe, Swiss-based researchers have performed integrative digital pathology and transcriptomic analyses of lung tissues of 16 coronavirus patients who died from respiratory failure during the first wave of Covid-19 and found striking histopathologic changes in the lungs.

'These two distinct patterns of immune pathology of pulmonary Covid-19 may give an insight into the natural progression of Covid-19 in the lungs,' said Professor Viktor Kölzer, head of the Digital Pathology department at the University of Zurich. The distinct patterns were defined by their differential expression of interferon stimulated genes (ISGs) and by their infiltration with immune cells/immune infiltration patterns. The ISG subgroups – termed ISGhigh and ISGlow – differ with regards to the characteristics and extent of pulmonary damage, pulmonary viral loads, immune infiltration, and time from hospitalisation to death.

'We combined digital pathology analysis for the quantitative study of immune cell infiltration in diseased lung tissue with transcriptomic analysis of key pathways involved in the immune response and PCR-testing of SARS-COV2 viral loads,' Kölzer explained

Integrative analysis

'This integrative analysis enabled us to detect and define two distinct immunopathological profiles of lethal Covid-19 based on gene expression and immune infiltration patterns. These profiles may point to distinct stages of disease progression with potential to guide specific therapeutic interventions.'

The ISGhigh profile showed high local expression of interferon stimulated genes and cytokines, high viral loads and limited pulmonary damage; while the ISGlow profile showed severely damaged lungs, low ISGs, low viral loads and abundant infiltrating activated CD8+ T cells and macrophages.

Patients in the ISGhigh group died at an early time point from a high viral load in the lungs as the immune system did not manage to suppress the virus. However, while ISGlow patients can initially defeat the virus, the activity of the immune response resulted in massive damage to the lungs and other organs and they died after several days or weeks.

'Patients who die early cannot adequately control SARS-CoV-2,' Dr Mertz, Senior Pathologist at the Institute of Pathology, Liestal, explained, 'while patients who die late suffer from diffuse alveolar damage and immune-pathology with increased lung remodelling. Infectious dose and individual predisposition to mount immune responses are likely to define whether or not a patient survives Covid-19.'

The autopsy data provided an important opportunity to better understand tissue damage patterns in lethal Covid-19 in the patient group, which was also high-risk due to age and other conditions, such as hypertension, heart disease and diabetes.

With the pandemic now in a second wave, the researchers have a 'pressing need to better understand the pathogenesis of Covid-19 for personalised risk stratification and treatment of critically ill patients.'

The collaborative study embraced molecular pathology, digital pathology, and bioinformatics, to deliver findings with potential clinical and biological implications and assess the immune response to Covid-19 from a multitude of aspects. Taking

Lung of ISGlow patient who initially defeated the virus but suffered massive damage to lungs and other organs due to the body's virus response and eventually died during the course of Covid-19

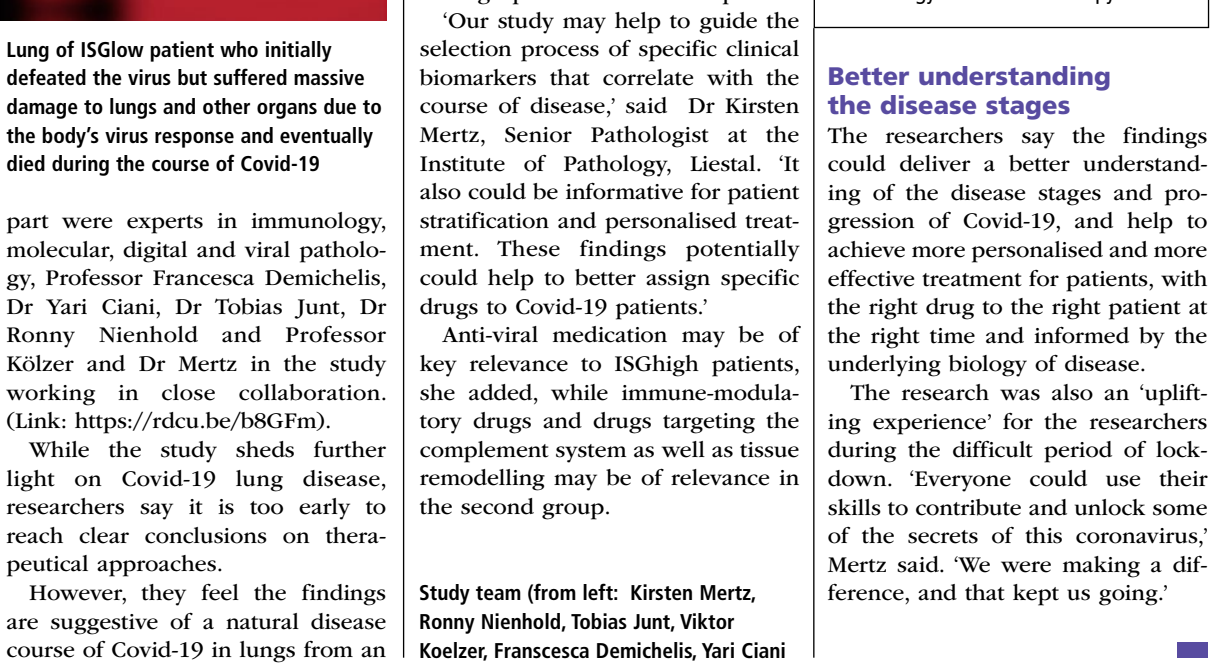
part were experts in immunology, molecular, digital and viral pathology, Professor Francesca Demichelis, Dr Yari Ciani, Dr Tobias Junt, Dr Ronny Nienhold and Professor Kölzer and Dr Mertz in the study working in close collaboration. (Link: https://rdcu.be/b8GFm).

While the study sheds further light on Covid-19 lung disease, researchers say it is too early to reach clear conclusions on therapeutical approaches.

However, they feel the findings are suggestive of a natural disease course of Covid-19 in lungs from an ISGhigh profile to a ISGlow profile.

'Our study may help to guide the selection process of specific clinical biomarkers that correlate with the course of disease,' said Dr Kirsten Mertz, Senior Pathologist at the Institute of Pathology, Liestal. 'It also could be informative for patient stratification and personalised treatment. These findings potentially could help to better assign specific drugs to Covid-19 patients.'

Anti-viral medication may be of key relevance to ISGhigh patients, she added, while immune-modulatory drugs and drugs targeting the complement system as well as tissue remodelling may be of relevance in the second group.



Study team (from left: Kirsten Mertz, Ronny Nienhold, Tobias Junt, Viktor Koelzer, Franscesca Demichelis, Yari Ciani

Dr Kirsten Mertz is a senior pathologist at the Institute of Pathology and Head of the Molecular Pathology and Cytopathology service at the Cantonal Hospital Basel, Liestal, Switzerland. Her research focuses on molecular diagnostics of cancer, immunopathology and the (molecular) pathology of infections.

Professor Viktor Kölzer is Attending Pathologist at the Institute of Pathology and Molecular Pathology, University Hospital Zürich; Assistant Professor and Lead for Digital Pathology, University of Zürich, and Honorary Senior Clinical Researcher, Department of Oncology, University of Oxford. His research aims to improve patient care through the implementation of high quality, science-driven, computational image analysis approaches with a focus on gastrointestinal disease, immunology and immunotherapy.

Better understanding the disease stages

The researchers say the findings could deliver a better understanding of the disease stages and progression of Covid-19, and help to achieve more personalised and more effective treatment for patients, with the right drug to the right patient at the right time and informed by the underlying biology of disease.

The research was also an 'uplifting experience' for the researchers during the difficult period of lockdown. 'Everyone could use their skills to contribute and unlock some of the secrets of this coronavirus,' Mertz said. 'We were making a difference, and that kept us going.'

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Post-Covid lung cancer screening in our 'new normal'

The slow return of mobile units

The coronavirus pandemic has had a severe impact on healthcare services but one area where that has been felt particularly deeply is with lung cancer screening. With sessions cancelled, treatment delays and social-distancing and safety requirements, many patients have been affected. However, as services begin to pick up again and lung cancer screening returns, three experts closely associated with the field offered their insights into what the future may hold under the 'new normal' for screening in the UK, Mark Nicholls reports.

Richard Booton is Consultant Respiratory Physician in the North West Lung Centre and Clinical Director for Lung Cancer & Thoracic Surgery at Wythenshawe Hospital in Manchester. He is also the Programme Director for the Manchester Lung Health Check Programme. His research interests include clinical care in thoracic oncology, advanced bronchoscopy and lung cancer screening. He is a member of the NHSE National Delivery Group for Targeted Lung Health Checks, and past member of the NHSE Expert Advisory Group on Lung Cancer Screening.

Ahead of the British Institute of Radiology's lung cancer imaging event, the three experts participated in a pre-session presentation and live Q&A entitled 'Relaunching a lung cancer screening service in the new normal'. Professor Richard Booton, Consultant Respiratory Physician in the North West Lung Centre and Clinical Director for Lung Cancer and Thoracic Surgery at Wythenshawe Hospital in Manchester, offered a clinician's insight into how lung screening has changed post-Covid. There were challenges in relaunching services within a community, he said, but, with reassurance to participants, the uptake remained high, though he acknowledged that the Covid-19 has impacted beyond community settings and into hospitals.

'In the diagnostic arena, the impact of Covid reduces our capacity, not least in CT scanning, lung function, bronchoscopy, CT-guided lung biopsies and PET scanning, and this is all a consequence of social distancing and requirement for Covid testing,' he added. 'In treatment terms having patients isolate, added time for donning PPE, reduced operating time, theatre access and anaesthetic availability, all have an impact. This creates an enormous propensity for delay, which was common pre-Covid and is going to continue to be common, if not exacerbated.'

Lack of screening infrastructure

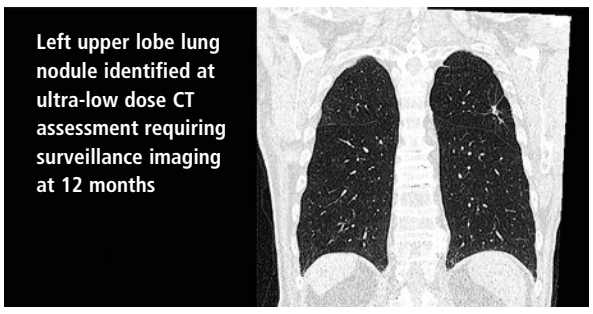
He pointed to a lack of screening infrastructure, the inability to get people quickly through the MDT (multi-disciplinary team) process and into treatment, and the UK's 'woeful' lack of CT capacity, as ongoing issues. Compliance to the 62-day target from urgent general practitioner (GP) referral to treatment continues to fall and he suspected that would get worse in the months ahead.

Booton said the pandemic had provided some 'illumination' on the difficult cancer screening landscape and highlighted the need to invest in workforce, diagnostics, to roll out faster pathways, and see more joined up collaboration in the UK's cancer alliances, as well as some centralisation in delivering complex pathways.

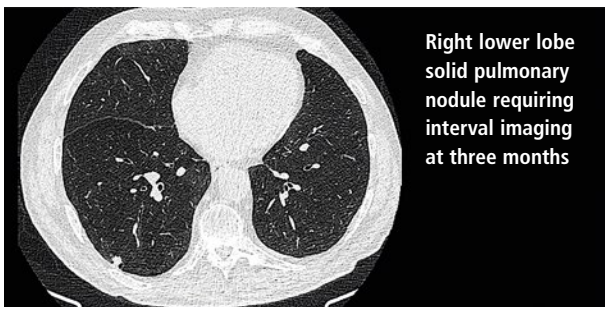
'Delay in lung cancer care,' he said, in conclusion, 'is not new but there is no doubt Covid will further compromise and slow care as capacity becomes a real problem. We need to fight for that capacity now as we enter the recovery phase – both within our hospitals and across our cancer alliances.'

The session also heard from Peter Sharpe, CEO of Cobalt Health – a charitable organisation which offers mobile lung cancer screening services – on the challenges of relaunching the service post-lockdown. In Manchester, during the year prior to lockdown in March, the organisation's mobile scanning units conducted 8,972 lung health checks (LHCs), including 4,555 low dose CT scans, found 88 lung cancers.

But in March, the programmes were paused and the charity's scanners went to support NHS England (NHSE) Covid-19 response by providing urgent oncology scans for hospitals across England.



Left upper lobe lung nodule identified at ultra-low dose CT assessment requiring surveillance imaging at 12 months



Right lower lobe solid pulmonary nodule requiring interval imaging at three months

Now, with the relaunch of the programme, the challenges are in maintaining social distancing, use of PPE, cleaning the equipment and also returning to previous locations, which were often in supermarket car parks, combined with a continuing high demand for CT across England.

Mobile scans on a supermarket car park

Some of the scan preparation processes, such as risk assessments, are being carried out by phone or video call and patients are invited to attend for mobile scans alone and scan-ready in their dress. Spirometry and blood pressure checks remain suspended. The scanners have enough space within to maintain social distancing, but supermarkets have been reluctant to allow the units back on their sites, though a unit has been situated at Manchester City's Etihad football stadium. Scheduled attendance has been lower to facilitate social distancing and there have been some same-day cancellations by patients who are nervous about venturing out as many have been shielding. But those willing to attend the mobile unit have been well-prepared and often feel more comfortable in a mobile screening setting than attending hospital. 'It is early days, but we still believe lung health checks will be an effective programme for lung cancer screening,' said Sharpe.

AI in lung cancer screening

Hasan Jouni, Business Development Manager, Siemens Healthineers, addressed the session about the role Artificial Intelligence has to play with some of the challenges faced in lung cancer screening, detailing how the AI-Rad Companion product chest CT and chest X-ray modules can help. He said they could be utilised to address backlogs in scan reporting and, while not providing a substitute for the radiologist, could help with routine, labour intensive, aspects of the workload by making in-roads into delays in reporting and improve turnaround time.

Significant advances in medical physics

Imagine: 30 radiation sessions reduced to five

To target ionised radiation as precisely as possible, imaging a tumour is vital in radiotherapy planning. 'Today, imaging is used increasingly during the therapy itself,' explained Professor Mark Ladd, Head of Medical Physics in the Department of Radiology at the German Cancer Research Centre (DKFZ) in Heidelberg, Germany, and President of the German Society for Medical Physics (DGMP), during the society's 51st annual meeting.

Interview: Daniela Zimmermann

This new imaging role is possible due to the magnetic resonance linear accelerator, MR-Linac for short, which combines a linear accelerator with a MRI scanner. 'It shows, in real-time, how the tumour moves with breathing,' Ladd explained during our European Hospital interview regarding current trends in medical physics.

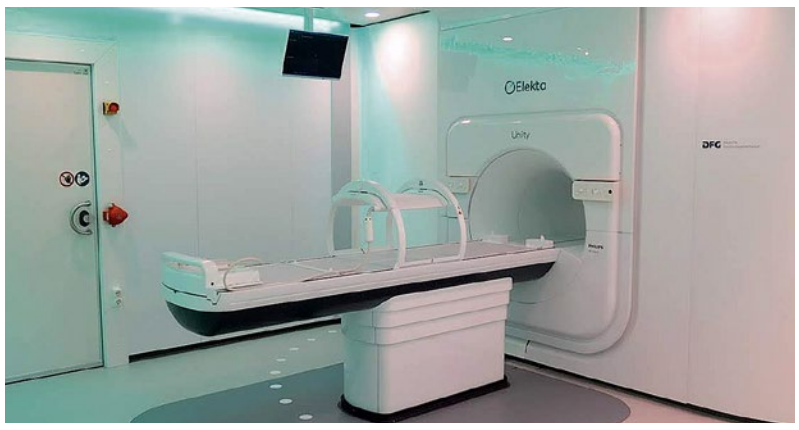
Continuous MR-Linac scanning during radiotherapy enables tracking of breathing-induced movement and thus adjust the therapy; it also records any change in location and size of the tumour during the weeks of therapy. 'Rather sooner than later, we'd like to control the collimators in real-time so as to adjust radiation in view of the changes, compared to the initial therapy plan. In short: we want to tailor the therapy plan in real-time,' Ladd underlined. The more precisely the tumour can be targeted, the higher the dose can be. 'Thus the patients wouldn't have to undergo 30 radiation sessions but maybe only five,' he pointed out. At DKFZ a project-team is looking for new approaches to adjust the collimators quickly.

Another research project in particle therapy deals with the exact recognition of the Bragg peak, i.e. the point when the energy of the ion beam reaches its peak and then sharply decreases. Since scientists are still uncertain where exactly the Bragg peak ends in the body, a comparatively large safety margin is defined around the tumour to reach as much of the tumour tissues as possible.

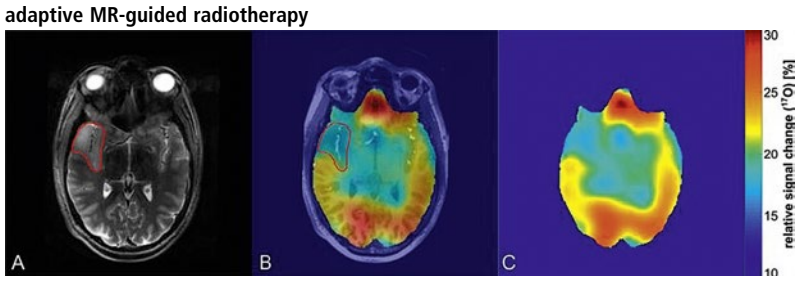
'With current technology the safety margin has to be so large that, in fact, we cannot realise the full potential of proton therapy,' Ladd reported. Thus, researchers are trying to develop different methods to determine the Bragg peak in vivo. One of these approaches tries to detect secondary gamma rays triggered by the proton beam in the body.

Better insights: photon-counting CT

Photon-counting CT is another remarkable development in radiology. DKFZ houses one of three CT prototypes worldwide that feature a unique component: a photon-counting detector made of a semi-conductor material that can directly convert X-rays into electrical signal impulses, making it particularly efficient. 'I do hope that this technology will one day be clinical routine,' Ladd said. While photon-counting detectors are expensive, they offer better resolution and allow imaging with significantly lower contrast doses. 'With regard to the current debate about contrast media, photon counting is a very promising approach,' he said.



MR-Linac (Unity, Elekta AB, Sweden) at the University of Tübingen (DFG ZI 736/2-1): a hybrid system combining a 1.5-T MRI scanner with a 7-MV linear accelerator for online adaptive MR-guided radiotherapy



Oxygen imaging at 7-Tesla

MRI with new elements and high field strength

Another trend in medical physics is X-core MRI. While in conventional MRI the spin of the hydrogen nucleus is measured, X-core MRI determines the magnetic moment of isotopes of other nuclei, e.g. sodium-23 (Na-23), oxygen-17 (O-17), potassium-39 (K-39) or chlorine-35 (Cl-35). Problem: these isotopes are rather rare. Only 0.04 percent of oxygen, for example, is O-17. In a DKFZ research project, patients inhale a gas enriched with O-17 during the MRI scan. The oxygen travels through the blood and as soon as it reaches the mitochondria in the cells and is converted into water it can be visualised.

'This enables us to precisely measure the local oxygen metabolism in the brain and in other parts of the body,' Ladd explained. Currently, one team is trying to detect whether regional differences in metabolism might indicate which areas of the brain will recover after a stroke and which ones won't.

Visualising the distribution of O-17 and other isotopes in MRI requires a field strength of 7-Tesla. Indeed, beyond this application 7-T MRI is one of the key development areas in medical physics. Since 2017, the first systems have been certified for clinical exams, initially limited to head scans and smaller joints. The advantage of a 7-T MRI scanner is not only resolution. 'There is an interdependence of sensitivity and time.' Ladd said, adding 'with a field strength of 1.5-T we can examine about everything that we can examine with 7-T – but at a much slower speed.'

3-T scanners are mostly used to perform exams faster than with a 1.5-T scanner. By contrast, a 7-T scanner not only reduces exam time but also offers enhanced spatial resolution and more detail. "You can compare it with standard and HD resolution of a TV screen: suddenly you see things you could not see before,' Ladd said. For example, the so-called swallow tails in the basal ganglia, whose lack indicates Parkinson's disease, can only be vaguely seen in a 3-T scan – but they are clearly visible in a 7-T scan.

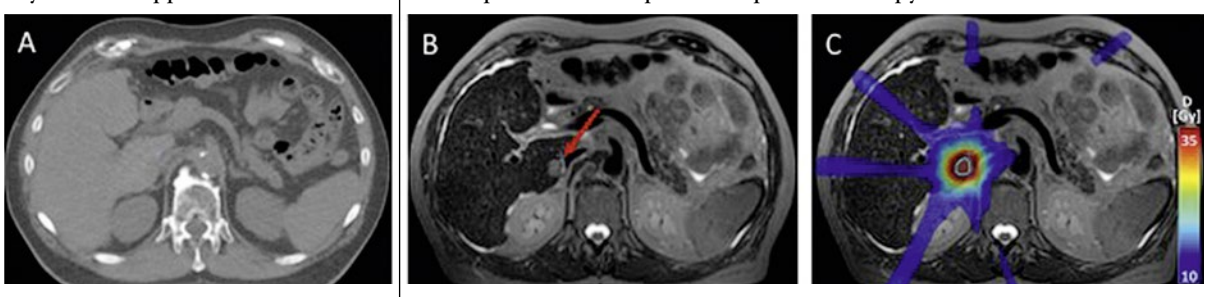
Gradient coils: pushing the envelope of physics

Ladd sees larger gradient fields as an overall trend in MRI. The faster the gradient, the higher the risk of peripheral nerve stimulation. This fact has limited the use of larger gradient fields. GE Healthcare, however, has developed a 3-T system for the head only, which is equipped with a faster gradient since, in head-only exams, the problem of nerve stimulation is less pronounced.

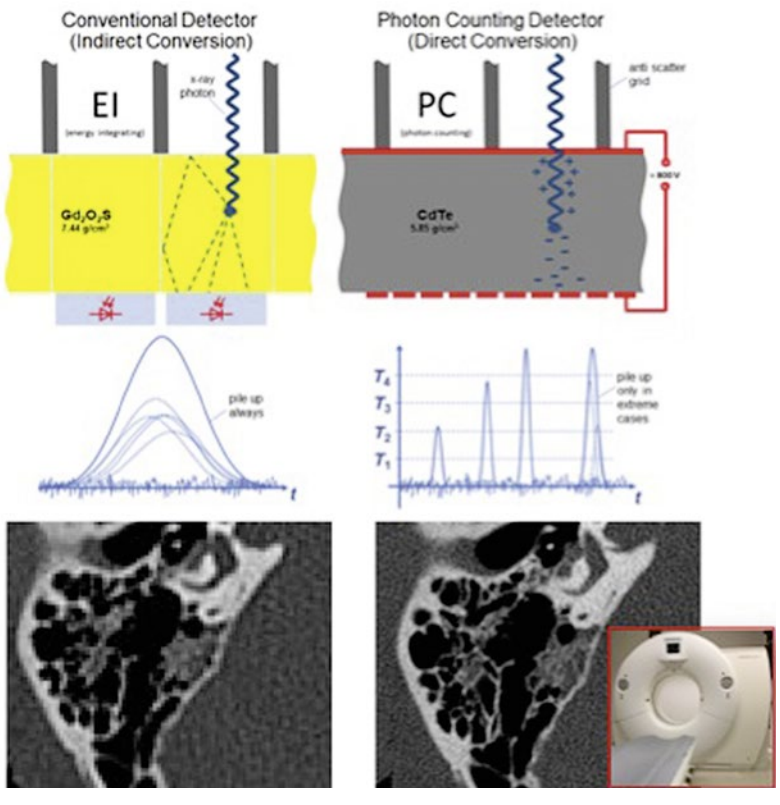
Some research teams have managed to simulate nerve stimulation caused by gradient coils prior to the actual scan. Before, the degree of nerve stimulation was measured using fully developed gradient coils and a performance cap for this particular coil was determined. Today, computer programs can predict the degree of peripheral nerve stimulation, thus the coils can be optimised in the development phase. 'Over the next few years, we will see significantly stronger gradient systems,' Ladd predicts.

PET-CT and the 2 metre detector

Last, but not the least in PET-CT, the first whole-body scanner may be in the wings. The Chinese company United Imaging developed a detector that measures two metres! Siemens is working on a system that combines four conventional detectors and thus enables a PET-CT scan of more than a metre. 'Whole-body PET-CT could open up new possibilities in imaging, which were unrealistic before due to the exceedingly high radiation exposure,' Ladd explained, 'including new options for visualising the course of a therapy.'



MR-guided high precision radiotherapy of a liver metastasis. (A) Native planning CT; target delineation is not possible without implanted markers or contrast agent injection. (B) Excellent visualisation of the target region using navigated T2-weighted MRI (red arrow). (C) Markerless MR-guided stereotactic body radiotherapy of a liver metastasis using the 1.5 T MR-Linac (Unity, Elekta AB, Sweden) 09/2020 at the University Hospital for Radiation Oncology Tübingen.



Photon-counting detectors are a major innovation in clinical CT. These directly converting detectors register photons and record their energy. Moreover, their pixels are much smaller than those of conventional detectors. The new technology promises spectral resolution comparable to dual energy CT, significantly smaller doses and greatly enhanced spatial resolution. The images of an inner ear were acquired with an experimental photon-counting whole-body CT scanner (Somatom CounT, Siemens Healthineers) at DKFZ

Having joined the German Cancer Research Centre (DKFZ) in Heidelberg in 2013, today **Professor Mark Ladd** heads Medical Physics in its Department of Radiology. He is also President of the German Society for Medical Physics (DGMP). His research focus is magnetic resonance imaging (MRI), particularly the launch and further development of new methods using ultra-high-field strengths and MRI in image-guided radiotherapy. He studied electrical engineering at the University of Michigan in Ann Arbor and Stanford University in California. In 1998, and received his doctorate from ETH Zurich in the context of a research cooperation project between the University Hospital Zurich and GE. In 2004 he became Professor of Biomedical Imaging at Essen University Hospital, where he increasingly focused on ultra-high-field MRI.

Presented at the Digital International Liver Congress

MRE plus Fib-4 jointly detect liver fibrosis

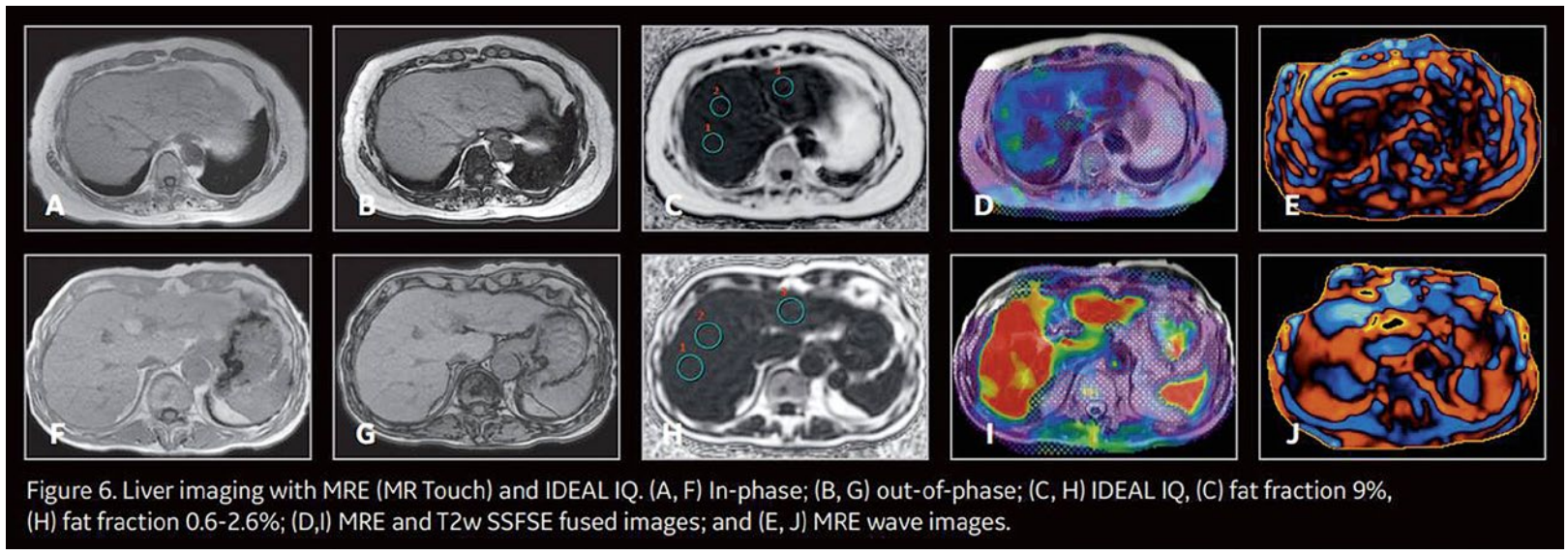


Figure 6. Liver imaging with MRE (MR Touch) and IDEAL IQ. (A, F) In-phase; (B, G) out-of-phase; (C, H) IDEAL IQ, (C) fat fraction 9%, (H) fat fraction 0.6-2.6%; (D,I) MRE and T2w SSFSE fused images; and (E, J) MRE wave images.

Jinho Jung is a researcher at the University of California, at San Diego NAFLD Research Center, with specific interests in various aspects of NAFLD, including non-invasive imaging, biomarkers and clinical trial design.

Rohit Loomba is Director of the NAFLD Research Center and leader of the study.

Rather than using techniques separately, researchers have determined that coupling image-based and serum-based biomarkers achieves a higher diagnostic accuracy in detecting stage two liver fibrosis, or above.

The study team, from the NAFLD Research Center, University of California at San Diego (UCSD), and colleagues at Yokohama City University in Japan, used magnetic resonance elastography (MRE) in tandem with the serum-based Fib-4 clinical prediction rule.

Their aim was to decide whether MRE alone, or combined with Fib-4, may be used for non-invasive identification of candidates for pharmacologic therapy among well-characterised patients with non-alcoholic fatty liver disease (NAFLD).

Their findings were presented virtually at the Digital International Liver Congress 2020 at the end of August by Jinho Jung of the UCSD NAFLD Research Center.

NAFLD is estimated to have a global prevalence of 25% and NAFLD patients with stage two fibrosis, or higher, have a significantly increased risk of progression to cirrhosis and liver-related mortality.

The gold standard for determining whether a patient is a candidate for pharmacologic therapy is liver biopsy, but this has limitations in terms of variability and discomfort.

Given the global burden of NAFLD, Jung said that liver biopsy assessment to decide candidacy for treatment of non-alcoholic steatohepatitis (NASH) related fibrosis is impractical. 'Therefore,' he added, 'there is an unmet need in the pathologic testing arena to accurately identify each fibrosis patient in a non-invasive manner with a high positive predictive value.'

There are currently some non-invasive diagnostic tests for detection of liver fibrosis, with image-based biomarkers such as Magnetic Resonance Elastography (MRE), Vibration Controlled Transient Elastography (VCTE), Sheer Wave Elastography (SWE) and Acoustic Force Radiation Impulse (ARFI). In addition, serum-based biomarkers include Fibrosis 4 (Fib-4), NAFLD Fibrosis score, Enhanced Liver Fibrosis score (ELF) and Fibrospect II. A combination of two unrelated biomarkers, such as image-based and serum-based biomarkers, has been proposed for staging of liver fibrosis and within the context of NAFLD, promising results have been shown to detect patients with advanced fibrosis or stage three fibrosis or higher.

Limited data

However, there are limited data on whether this data or clinical prediction rule can be applied to stage two fibrosis or higher patients and its cut points.

To explore this, the – 'Utility of magnetic resonance elastography in accurate identification of candidates for pharmacologic treatment of NASH related fibrosis: a prospective cohort study' – aimed to examine whether MRE alone, or in combination of Fib-4, may be used for non-invasive identification of candidates for pharmacologic therapy among well characterised patients with NAFLD with liver biopsy assessment using NASH CRN histologic scoring system as the reference standard.

Findings, which underlined the value of MRE in this context, were validated in a geographically and ethnically diverse external independent validation cohort with collaborators in Yokohama.

The UCSD cohort of 238 patients with a range of ethnicities had 170 with stage 0-1 and 68 had fibrosis stage two or higher. The validation cohort in Japan recruited 222 patients with stage 0-1 and 138 fibrosis stage two or higher. Jung said: 'We found that MRE is more accurate than routinely available current prediction rule Fib-4 in detecting stage two fibrosis or above. The difference was clinically and statistically significant.'

Positive predictive value

Combining MRE with FIB-4 (MRE≥3.3kPa and FIB-4≥1.6) to develop a clinical prediction rule to rule in ≥stage two fibrosis patients showed a positive predictive value (PPV) of 97.1% in the UCSD-NAFLD cohort, and remained significant at 91.0% in the Japan-NAFLD cohort. It is important to note that the cut-points were determined through UCSD-NAFLD cohort and then were validated in the Japan-NAFLD cohort.

'By coupling MRE and Fib-4 we could achieve higher diagnostic accuracy compared to MRE and Fib-4 alone,' said Jung. 'With the cohort being geographically and ethnically diverse, this stresses the clinical applicability of these results in a western and eastern population.'

He acknowledged that there are caveats and limitations to the findings and the findings are only recommended for usage in hepatology clinic settings to rule in patients for pharmacologic treatments.

'As cut points may be different in primary care settings,' he said, 'further study needs to be done in a primary care or diabetes clinic.'

Jung concluded that this study – led by Professor Rohit Loomba, Director, NAFLD Research Center – will serve as a clinical prediction rule to give a high positive corrective value for clinicians to rule in patients to reduce the burden of patients for avoidable risk of liver biopsy. (MN)

French radiologists set their eyes on the stars

Anatomy meets astronomy

About 2,200 satellites are currently orbiting the Earth and soon space stations may be equipped with the latest medical imaging technology, including interventional radiology devices.

In France, radiologists and astronauts are putting their heads together to make this vision materialise in a unique partnership between the French Society of Radiology (SFR) and the French Space Agency (CNES).

Alain Luciani, President of the JFR 2020, the SFR's annual meeting, explained how this alliance could help not only advance healthcare in space but also knowledge of space travel's impact on the body and population health.

'Human spaceflights beyond the Earth orbit and to the Moon and Mars trigger an accelerated but potentially reversible ageing process,' explains radiology Professor Luciani. 'Strain on the body is multiple, impacting not only the MSK system but also the central nervous system, with ocular complications.'

Advanced imaging techniques can help to anticipate, understand and potentially correct disorders resulting from travelling into and back from space. MRI or CT can help evaluate bone density, reduction of the muscular mass and modifications of the cerebrospinal fluid, which are also challenges for population health. For example, muscular mass evaluation is a relevant prognostic marker for patient survival in oncology, as recent studies on sarcopenia have shown.

'The perspective of human spaceflights raises the questions of monitoring astronauts' health and potentially implementing remote treatment. The SFR wishes to bring its expertise to develop innovative and miniaturised technology to help monitor astronauts' health beyond current use of ultrasound devices, and transfer interventional radiology techniques, i.e. minimally invasive procedures, to help treat emergencies directly inside inhabited spaceships and stations,' said Luciani

Ultrasound experience aboard the International Space Station (ISS).

Are you considering sending radiologists into space?

We can ask that question; it has already been tackled in the literature (Kansagra et Coll. JVIR 2015;26:825-828). But beyond this discussion, we want to promote the development of remote monitoring tools and bring our expertise to accompany space travels from Earth and create training programs with expert radiologists.

What is the risk of ionising radiation?

Cosmonauts and astronauts are exposed to ionising radiation, cosmic rays, galactic rays and particles that are emitted by solar eruptions and Van Allen belts when in orbit around the Earth. These so-called heavy rays are very different from the low dose radiation that is emitted by radiological devices on Earth.

Nonetheless, the development of radiation protection tools for astronauts is a shared preoccupation for both the SFR and the CNES.

Here again, space is a model to appreciate the effect of both heavy particles, which are rather applied in radiotherapy, and chronic exposure to lower intensity radiation, which is more similar to the exposure to ionising radiation induced by X-ray-based diagnostic radiology.

There is also an issue concerning equipment, notably radiation protection strategies and imaging equipment selection, since X-ray sources have not yet been embarked during space travels, except in miniaturised osteodensitometry projects for animal testing. These challenges can be transposed to patients on Earth, notably through the development of miniaturised sources and devices that could one day be used, for example, close to intensive care beds, as patient travel is increasingly complex.

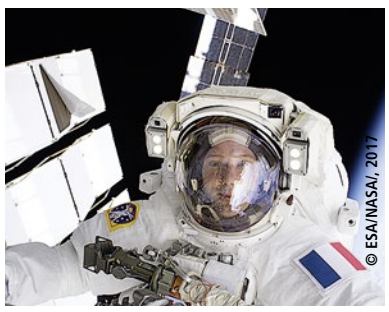
What about interpreting images from space?

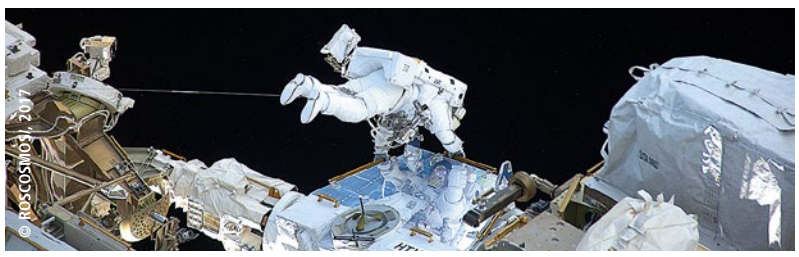
Space offers exploration possibilities for teleradiology, to which French radiologists wish to make a substantial contribution. Sharing complex data, such as radiological images on long distances, opens investigation in data accelerated transmission and compression, without losing imaging data, which can also be applied on Earth, for example remote radiology services for places difficult to access.

Will the partnership tackle celestial as well as human images?

The CNES produces Earth images that are acquired from space and space images to explore the universe. The agency must therefore handle huge quantities of data, develop autonomous image analysis

Everywear experience on board the International Space Station





Left: French aerospace engineer, pilot and European Space Agency astronaut Thomas Pesquet in his spacesuit on a spacewalk. Below: Thomas Pesquet spacewalking during the Proxima mission.

Radiologists must learn to distinguish signs of two arteriopathies

Deterring paediatric acute stroke

Acute stroke in children has the same incidence as brain tumours and can seriously affect a patient's life. Two kinds of arteriopathies are common drivers of paediatric acute stroke and radiologists must learn to distinguish their signs as early as possible to improve prognosis, according to Béatrice Husson, a paediatric radiologist at Le Kremlin Bicêtre Hospital in Paris.

Report: Mélisande Rouger

'Acute stroke can trigger focal motor deficit in so-far healthy children. There can be diagnostic wandering because deficit, before being definitive, can regress and fluctuate for many hours or even days, and because knowledge of this ischemic aetiology is still insufficient and wrongly attributes diagnosis to migraine or epileptic seizures with Todd's paresis,' said Husson at the recent JFR, the French Society of Radiology's annual meeting, online.

Unlike adults, a leading cause of acute stroke in children is arteriopathy, especially focal cerebral arteriopathy, which causes 30 to 40% of paediatric strokes, with unilateral damage of anterior circulation, and vertebral arteriopathy, a less common yet typical condition of the paediatric age.

'The first thing to remember when imaging a child with suspected stroke is to avoid using sedation, which could complicate patient neurological monitoring and is no longer necessary given the important reduction of acquisition times in MRI,' she advised.

Tending to the child in a calm and comforting atmosphere without losing time is paramount. MRI is the first choice modality in these patients, except when they present with consciousness disorders. "In this case,' Husson added, 'we'll carry out a CT scan with an anaesthetist resuscitator at our side.'

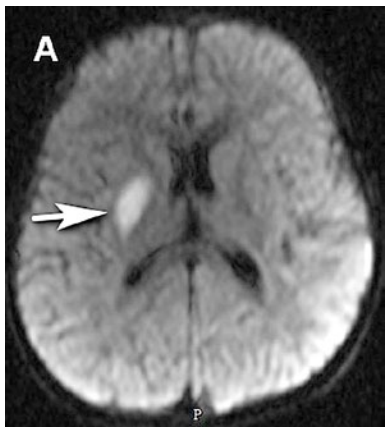
MRI protocol includes a diffusion sequence, T2 or magnetic susceptibility sequence, FLAIR axial study, TOF MRA at the level of the circle of Willis, MRA of cervical arteries, non-contrast perfusion – if possible – and a T1 sequence.

For CT, radiologists should perform non-contrast head CT, followed by arterial CT angiogram of the head and neck.

Husson shared several clinical cases with the audience, including the images of a child presenting with deep left ischemic stroke and occlusion of the left middle cerebral artery. Thrombectomy was initiated and recanalization looked satisfying on angiographic images before and right after procedure, however following MRI showed renewed occlusion and stroke extension a few hours later.

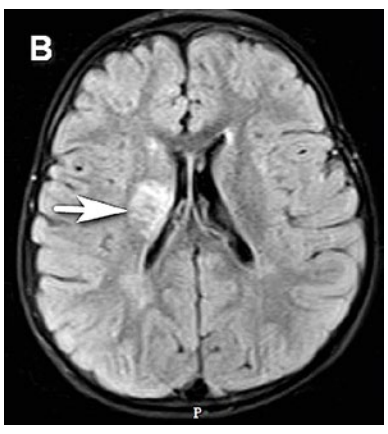
'This evolution, and these possible complications, can be explained by the aetiology of this focal brain arteriopathy, which we believe is linked to arterial wall inflammatory damage that may be caused by infection. The most common infectious agents are varicella and zona viruses, and so we will systematically look for varicella infection 12 months before stroke in a child presenting with such symptoms, ' Husson explained.

MRI follow-up was able to show recovery and stabilisation of arterial lesions, enabling an end to antiplatelet treatment 18 to 24 months after the event. The second arte-



Two and a half year old boy. Left hemiplegia discovered as the patient woke in the morning. Varicella episode had occurred four months before neurological event. Acute stroke in the deep right middle cerebral artery (MCA) secondary to focal arteriopathy, probably post infectious (varicella)

Figure A: axial diffusion sequence. Hypersignal of the right lenticular nucleus (arrow) linked to acute stroke in deep right MCA



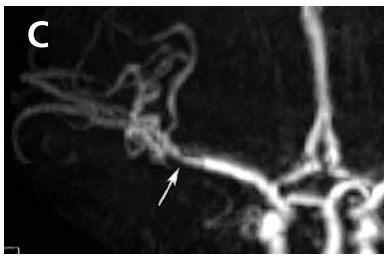
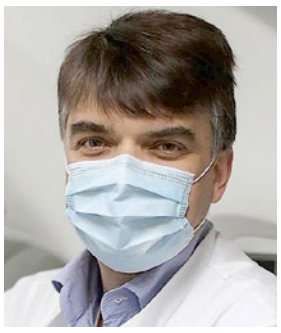


Figure B: Flair T2 sequence. Hypersignal of the right lenticular nucleus (arrow) confirming constituted stroke four hours earlier

Figure C: Face reconstruction of the Willis polygon (acquisition with a TOF MRA sequence), showing distal stenosis of the M1 segment in the right MCA (arrow)



Alain Luciani is full professor of radiology at the University Paris Est Creteil (UPEC), working at the Imaging Department of University Hospital Henri Mondor, the second largest University Hospital in Paris, where he is the medical director of the Therapeutic Interventional and Imaging Functions department. He is President of the JFR 2020 and Vice President of the French Society of Radiology (SFR) and a former General Secretary of the National College of Academic Radiologists in France (CERF), as well as former President of the French National Abdominal Imaging Society (SIAD).

tools and extract information from so-called weak signals.

These concerns align with those of the radiologists' regarding image management and analysis tools to improve patient image data evaluation. We also deal with large and constantly increasing quantities of data and are looking to use AI to improve image quality (through denoising) and mine information from weak signals, in order to advance predictive imaging, which was one of our highlights at the JFR 2020.

'Our common goal is to promote scientific interactions between our researchers, to improve and speed up innovation transfer between our fields with these image analysis tools. We use similar tools to handle Earth images obtained from space and patient images acquired with MRI or CT in many instances, such as image denoising and automated information extraction. (MR)

Béatrice Husson is a paediatric radiologist at le Kremlin Bicêtre Hospital (Groupe Hospitalier APHP Université Paris Saclay) in Paris, France. Throughout her career she has specialised in paediatric neurovascular malformation pathologies and rare paediatric brain inflammatory disease. Since 2013 she has been a referring radiologist for the National Referring Centre for Vascular Stroke in Children led by Dr Manoëlle Kossorotoff

riopathy radiologists should suspect in children with acute stroke is vertebral arteriopathy. In this setting, stroke typically occurs in the posterior circulation with multiple parenchymal lesions in 40% of cases that are associated with localised arterial lesions in segments V2 and V3. 'From this pathological area in the vertebral artery, embolus may cause basilar or posterior cerebral artery thrombosis,' she said.

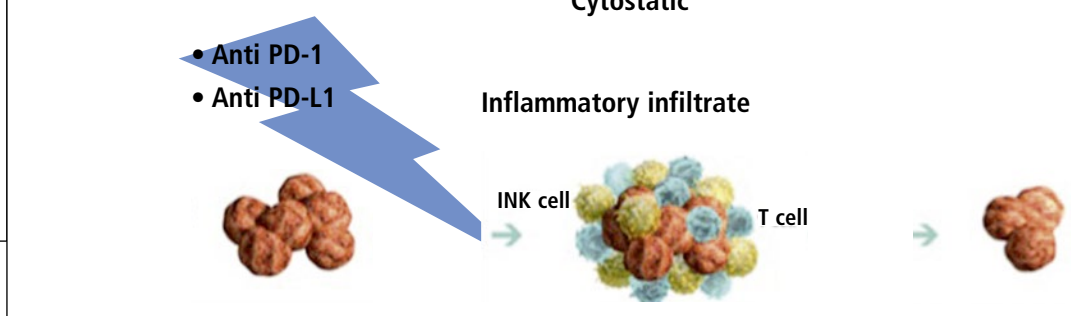
To properly explore this arteriopathy, radiologists should perform additional, thin-sliced T1 SAT cervi-

Continued on page 19

Lung cancer update

Immunotherapy, iRecist and complications

Dr Charlie Sayer is a consultant radiologist at Brighton and Sussex University Hospitals Trust in the south of England, with an interest in thoracic, head and neck and oncological imaging. He completed a two-year fellowship in cardiothoracic and body imaging in London during which he conducted academic work in lung cancer surveillance imaging, pulmonary hypertension and interstitial lung disease. Recently, he has co-authored book chapters and papers on lung nodule imaging, interstitial lung disease, pulmonary hypertension, lung cancer screening and pericystic lung cancer.



Report: Mark Nicholls

The evolving area of immunotherapies in lung cancer and the role of iRecist treatment assessment protocols were investigated during a virtual session organised by the British Institute of Radiology (BIR).

Consultant radiologist Dr Charlie Sayer, specialist in lung cancer imaging at the Brighton and Sussex University Hospitals Trust, South of England, focused on immunotherapies, the limitations of traditional response assessment, and the role of iRecist in the context of NSCLC (non-small-cell lung carcinoma), and also examined assessment of immune-mediated toxicities and what radiologists need to be aware of in this post-Covid-19 pandemic.

The session was part of a BIR lung cancer study day, 'Lung Cancer Imaging: Update for the not-so-new normal', which provided updates in lung cancer imaging.

In his presentation, 'Immunotherapy, iRecist and complications in NSCLC (in a post-Covid world), Sayer said: 'Cancer has an ability to avoid immune detection, now known as emerging hallmark malignancy. Essentially, we are aware it can express certain cell receptors which can evade the immune system, essentially telling the immune system there is nothing to see.'

Sayer pointed to a study of resected lung cancers and how in cancers with high immune evasion capacity the prognosis was significantly worse. Immune checkpoint inhibitors have been developed to target these pathways and work by activating T cells that have been suppressed or evaded the tumour. Receptors of most interest in lung cancer are PD-l1 and PD1, with Pembrolizumab the most commonly used agent in the UK.

'What we are seeing is patients with Stage 4 NSCLC, previously treated with chemotherapy or radiotherapy, with up to 20% now achieving survival up to five years,' he said. "This is even better if we look at patients who are treatment naïve and receiving immunotherapies, with around half having an overall survival of two years.'

Chemo and immunotherapy combined

Good radiological responses are also being seen with combinations of chemo and immunotherapy, Sayer added. Looking at response assessment, he referred to Millar's criteria from the 1980s with a 'common language' to describe radiological effects in clinical trials, WHO guidelines and Recist and Recist 1.1, but he stressed: 'It is important to note that these were never intended for use outside clinical trials and have limitations in practice.'

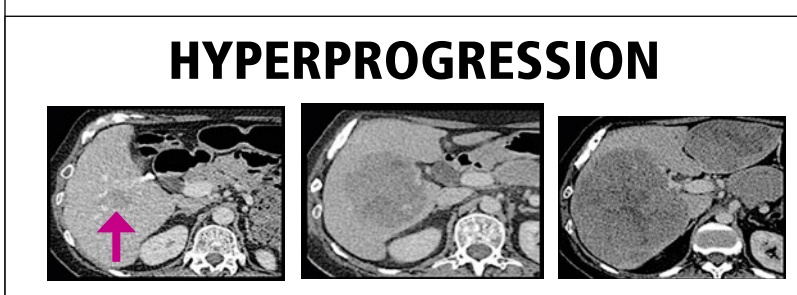
As tumours respond differently to immunotherapies compared to chemotherapies, the iRecist consensus guideline was developed by the Recist working group for the use of modified Response Evaluation Criteria in Solid Tumours (Recist version 1.1) in cancer immunotherapy trials, to ensure consistent design and data collection and facilitate the ongoing collection of trial data.

Sayer, who noted that Recist 1.1 has limitations for immunotherapy response assessment, explained that a number of tools have been developed to look at immunotherapy response to avoid the potential premature cessation of therapies and to capture atypical responses. 'The most recent iteration is iRecist, which was published in 2017, and we are now using this in clinical trials. iRecist may seem intimidating but is actually very simple. If you are familiar with Recist 1.1 it is the same definitions that are used for assessment until we see a progression radiologically; from that point iRecist begins.'

Hyperprogression is an important concept with rapid progressive disease following initiation of immunotherapy and is associated with poor outcome, he pointed out and also touched on immune-related toxicities and immune-related pneumonitis. 'If we think of the immune system being in a delicate balance, too much immune function can result in autoimmune disease, too little immune function can leave us susceptible to infection or malignancies,' he said. 'Immune related pneumonitis is more common in NSCLC patients, and associated with increased mortality. It is the most important immune-related adverse effect to be aware of in lung cancer patients because of its ability to worsen the overall prognosis.'

There are also post-Covid-19 considerations, with the pandemic having increased the complexity of cancer care.

'This is now a balancing act – in balancing the risk of treatment delay versus harm from Covid-19,' Sayer observed. The disease, he said, is no worse having Covid-19 while being treated with immunotherapies, and this might be to do with 'ramping up' the immuno-system. Immunotherapy is now deemed by the NHS as a Covid-friendly cancer treatment. 'This is because of its ease of delivery, it can be given orally, in the community or at home, and the ability to have treatment pauses on patients who have received immunotherapy for some time.'



Improving men's infertility diagnosis

Multiparametric ultrasound finds causes

Infertility has long been attributed to women alone, but medical advances have shown it really is a couple's problem, with 20% of couples presently having trouble conceiving. Medical imaging, in particular ultrasound, can help identify underlying causes of men's infertility and other related health issues, an Italian radiologist explained during the last European Congress of Radiology.

Multiparametric (MP) ultrasound is the imaging modality of choice to evaluate findings that, when cross-checked with patient history and physical and laboratory examinations, can help identify potential causes of infertility in men.

'The presence and site of an obstruction of the seminal tract, testicular volume and characteristics, cryptochidism – absence of one or both testes – varicoceles and focal lesions can all be assessed with MP ultrasound,' said Michele Bertolotto, Associate Professor of Radiology at the University of Trieste, Italy.

A complete examination

The examination must be performed carefully to evaluate size, echogenicity and echotexture of testes; size and morphology of the epididymis; and evaluation of the vas deference, prostate, seminal vesicles and ejaculatory ducts. The best way to evaluate volume of testicles is possibly using the Lambert formula, according to Bertolotto.

In patients with testicular causes for infertility, MP ultrasound enables to evaluate cryptorchidism, and to pick changes in the testicular parenchyma resulting from chromosome abnormalities, orchitides and ischemic disease.

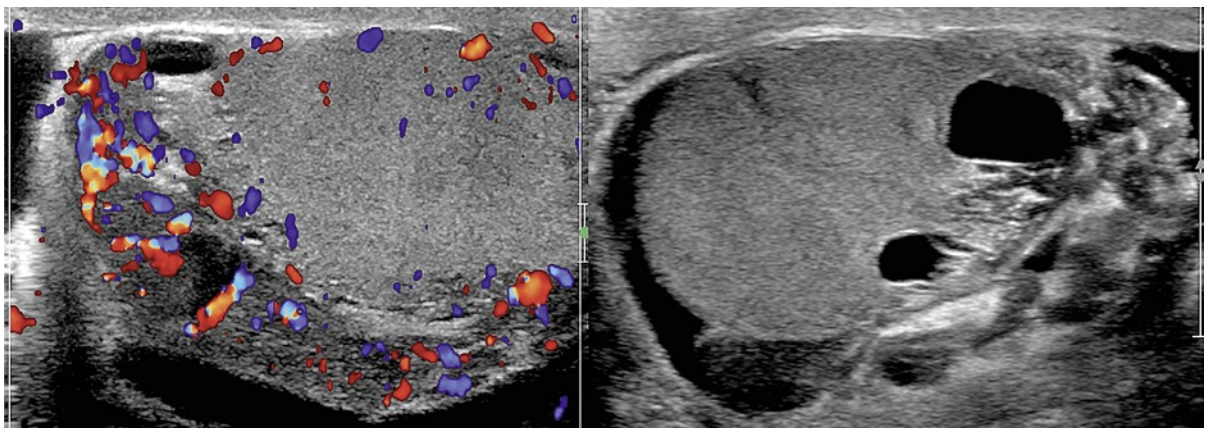
In cryptorchidism, the modality helps identify the testes at the level of the inguinal canal and also sometimes at the level of the abdomen. In some instances, MRI may help better identify cryptorchidism because of high signal intensity on T2 weighted images and diffusion-weighted images.

However, radiologists must remember that when the testis is markedly hypothrophic, signal intensity in diffusion-weighted imaging is reduced. 'Sometimes findings are more visible on ultrasound than MRI,' he pointed out.

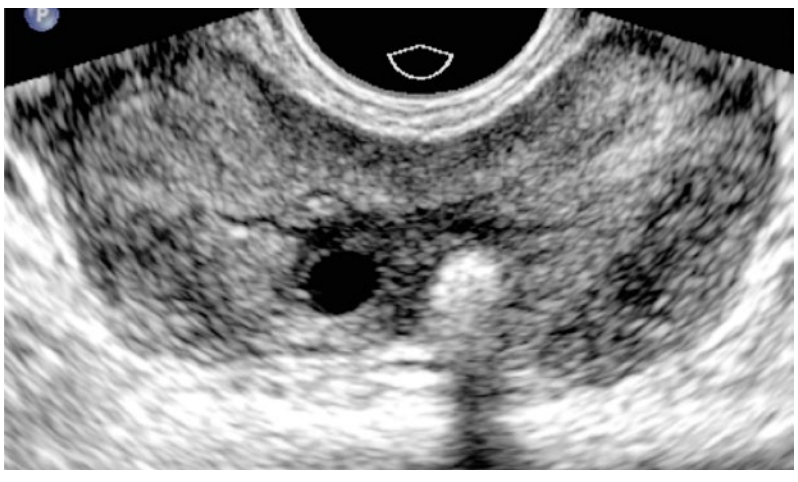
In obstructive causes of infertility, ultrasound enables careful evaluation of the entire seminal tract, and can help spot congenital abnormalities and the obstruction site.

'An epididemal head larger than 11mm can be considered a sign of obstruction if the level of epididymis and other causes of obstruction of epididymis are chronic epididemitis,' he explained. 'Cysts, interruption and stenosis may also be identified as signs of obstruction.'

MP ultrasound can also show obstruction in vas deferens and seminal vesicles, helping among others to recognise agenesis, a rare malformation commonly associated with other abnormalities, such as absence of a vas deferens or absence of a kidney.



Chronic epididymitis causing obstructive infertility. The epididymis is enlarged and hyperemic. Obstruction is demonstrated by presence of dilated rete testis with intratesticular spermatoceles



Azoospermia caused by obstruction at the level of the ejaculatory ducts. The right duct is dilated, due to distal stenosis (not shown). The left duct is obstructed by a stone

Obstruction in the ejaculatory ducts may be caused by stenosis, stones or cysts, which can also be clearly shown by ultrasound.

New European guidelines for varicoceles

Varicoceles are varicose veins of the testicle and scrotum that may cause pain, testicular atrophy or shrinkage, or fertility problems. Varicoceles are a common urological problem and are often detected incidentally.

The disease affects about 10 percent of all men and 30 percent of men among infertile couples; but the condition also can be corrected.

'Varicoceles are the commonest potentially correctable cause for men's infertility. However there is a lot of confusion in the literature about how to perform the corresponding ultrasound examination and report it,' he said.

Earlier this year, the Scrotal and Penile Imaging Working Group of the European Society of Urogenital Radiology (ESUR-SPIWG) has released guidelines and recommendations on how to perform MP ultrasound for varicoceles.

The publication details how the examination should be performed in supine and erect position, at rest and during Valsalva. 'Bilateral, grey scale, colour and spectral analysis should be used. Testicular and size of the largest vein should be measured; reflux is considered pathological when longer than two seconds,' Bertolotto said.

Reporting should mention testis volume, echogenicity and echo-

Smartphone aids learning of brain US scans semeiotics

Neurosurgical oncology

Italian neurosurgeon Professor Francesco Di Meco, explored the current and potential role of intra-operative ultrasound in neurosurgical oncology during the annual meeting of the European Association of Neurosurgical Societies (EANS) this October.

The extent of resection is considered a prognostic factor in operative neuro oncology surgery and image-guided surgery is being regarded as one of the major aids to increase the extent of resection of brain tumours.

Image-guided surgery techniques include neuronavigation, intra operative MRI, fluorescence and intra-operative ultrasound (US). The latter presents with several benefits during and after surgery, although it remains an unusual imaging technique for neurosurgeons, according to Francesco Di Meco, full professor of neurosurgery and maxillofacial surgery at Milan State University and head of the department of neurosurgery at C. Besta Neurological Institute Foundation in Italy.

Real-time and dynamic

'Intra-operative US is a real-time, dynamic and relatively inexpensive imaging technique. The improvement of the resolution and quality of images enables distinguishment between grey and white matter,' he explained. Real time imaging is useful for anatomic structures identification, a challenging task even for very experienced neurosurgeons.

The fusion of neuronavigation and intraoperative US has helped understanding the semiotics – the study of signs and symbols and their use or interpretation – of ultrasound, and a number of softwares have been validated that combine the techniques, such as the Orion H2/US and Virtual Navigator.

This fusion may also help to correct one of the major drawbacks of neuronavigation: brain shift. 'With neuronavigation,' he explained, 'two blended images of the tumour are not perfectly overlapping, there's a gap.'

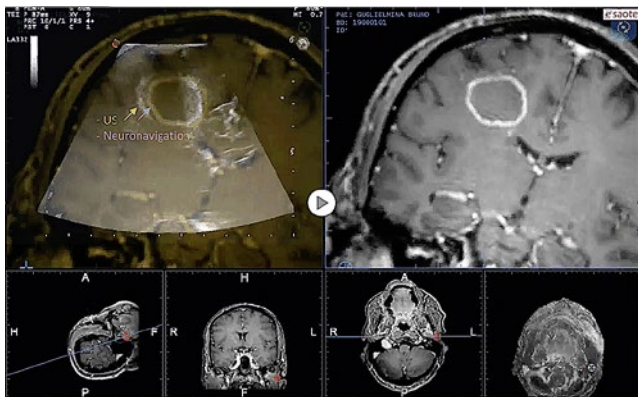
To correct this, surgeons can freeze one of the images, for example the MRI's, and draw it over the image provided by ultrasound, and can repeat the operation as many times as necessary. 'Having real-time images is useful at any point during surgery. You can check at any time how much tumour is left. And you can also check the end of resection, if there are some remnants of the tumour,' Di Meco pointed out.

Evolving role

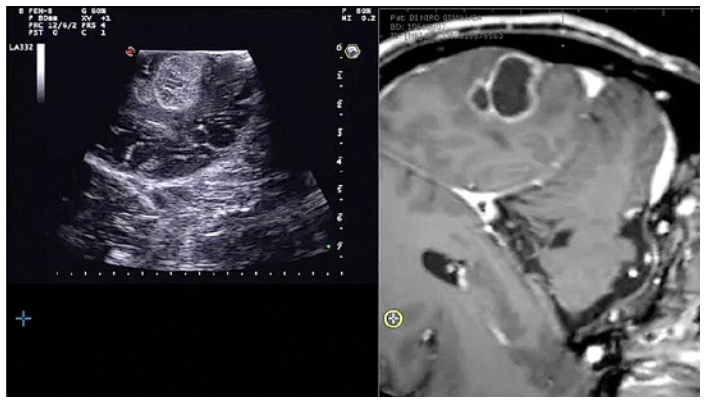
The neurosurgeon tackled the evolving role of intraoperative US with features such as Doppler, elastosonography and the use of contrast.

Doppler enables the identification of vessels, notably those that have been impacted in tumour resection, while elastosonography provides information about stiffness of the tissue, using the colour reference scale to evaluate hard or soft tissue.

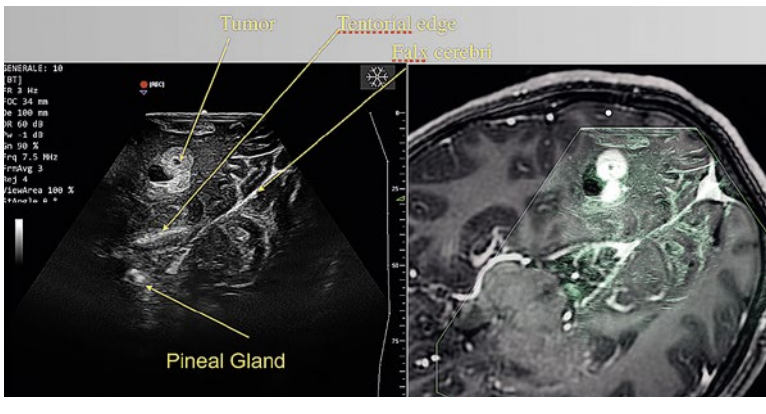
Elastosonography can also help to identify the borders of a tumour. 'We found that elastosonography is superior to B-mode ultrasound for the definition of margins,' he said. Research has shown that elastography is also useful to identify tumour remnants at the end of resection.



Brain shift correction



Integrated intraoperative MR/US neuronavigation



Real time images for anatomical landmarks identification

Michele Bertolotto is Associate Professor at the Department of Radiology, University of Trieste, Italy. Bertolotto was born in Genoa, Italy. He has been working at the department of Radiology of the University of Trieste since 1996. He currently devotes the majority of his time to clinical practice as senior consultant in genitourinary radiology. His research activity concerns several fields of diagnostic imaging. Contributions are mainly on abdominal and genitourinary radiology. Bertolotto has several commitments in the European Society of Radiology. He is currently serving as ESUR secretary/treasurer.

texture; abnormalities; presence of varices; diameter of the largest vein, and changes of flow at colour and spectral Doppler, according to the patient's position.

It is not mandatory to classify varicoceles, but when it is, the Sarteschi's grading should be used, as it is the most complete and widely used classification in Europe.

When performing MP ultrasound for infertility, radiologists will often find incidentally impalpable focal lesions, which most of the time are benign, Bertolotto stressed. 'Physicians should be aware that infertility is a risk factor for developing testicular tumours, but they must also know that the majority of focal lesions discovered with ultrasound are benign or non-neoplastic. Therefore,' he concluded, 'a conservative approach should be proposed initially.' (MR)

Francesco Di Meco is full professor of neurosurgery and maxillofacial surgery at the department of pathophysiology and transplantation in Milan State University, Italy. He also heads the Department of Neurosurgery at the C. Besta Neurological Institute Foundation (Fondazione Istituto Neurologico C. Besta) in Milan.
Di Meco is among the world's leaders in intraoperative ultrasound in neurosurgery and has founded the first neurosurgical simulation centre in Europe, the Besta Neurosurgical Simulation Centre, which is one of the best-equipped simulation centres in the world.
He has published more than 190 peer-reviewed papers and several book chapters (h-index: 50, Scopus) focusing on neurosurgical oncology and has gained considerable experience in the loco-regional treatment of brain tumours.
the professor is also a co-author of the first international research that led to the identification of tumour stem cells in glioblastomas and alternative treatment strategies by inducing tumour cells differentiation.

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Deterring paediatric acute stroke

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cal sequence to look for wall haematoma because dissection must be suspected.

In addition to MRA at the level of the circle of Willis, it is mandatory to perform high quality cervical MRA, Husson explained. 'I would recommend carrying out non-injected, cervical-centred TOF rather than injected SAT, which may prove complicated due to patient movement triggered by the injection, the combination of venous and arterial time and wide field study, which is not adapted to children's small-sized vertebral arteries. If cervical MRA fails, then we'd be looking at an angio CT at arterial time. When none of these examinations help reach diagnosis, we may consider performing conventional angiography,' she said.

A major risk of vertebral arteriopathy is recurrence, which is five times higher than in focal cerebral arteriopathy. Recurrence mainly occurs in the first three months after stroke and justifies anticoagulant treatment. In conclusion, one must remember high incidence of arteriopathy causing acute paediatric stroke. 'Recanalisation treatment for unilateral focal arteriopathy with middle cerebral artery stroke and transitory inflammation at carotid T level can be discussed case by case. Recurrence may occur and justifies monitoring. After arterial stabilisation that is confirmed by MRI, antiplatelet treatment can be interrupted. The other arteriopathy radiologists must suspect is vertebral arteriopathy, which justifies maximal examination of vertebral arteries because this typical lesion affecting the segments V2 and V3 is highly suspicious of embolus that can cause basilar occlusion. 'This finding,' she concluded, 'justifies thrombectomy whenever technically possible, and frequent early recurrence justifies initial anticoagulant treatment in children.'

HartKliniek – cardiology with a Dutch twist

Cardiology tends to be surrounded by a maze of regulations, responsibilities and red tape. Leave it to the traditionally mercantile Dutch to streamline things. Case in point: HartKliniek, a chain of medical specialist diagnosis and treatment centres in the Netherlands which aim to transform cardiology to a more effective model – less personnel, more time for patients. We spoke with Menno and Willem Baars, members of the founding trio, about the origins of the HartKliniek and how paring down structures to the essentials can benefit patient wellbeing.

HartKliniek was founded in 2014 by CEO Menno Baars, his brother Willem Baars as COO and CMO Chris Hie. Today, there are eleven centres under the group's name located in Almere, Amsterdam, Den Haag, Dronten, Groningen, Hoorn, Lelystad, Nijmegen, Vlaardingen, Oisterwijk and Zandvoort, with 20 cardiologists employed. In 2019, more than 20.000 patients were treated, with an expected growth to 30.000 in 2020. The goal is to establish several locations in each of the 12 Dutch provinces to support the notion of 'bringing cardiology to the neighbourhood'.

Cardiologists stretched to the max

The fundamental idea behind HartKliniek is surprisingly old-fashioned: paying more attention to the individual patients. One evening, at the end of his working day at the hospital, cardiologist Menno Baars was fed up with spreading his working hours across 50 patients – clearly too many to treat with proper diligence in an eight-hour shift. Excessive time pressure had led to the fact that frequently, he observed, the correct diagnosis was not made during the first work-up and the cardiologists had to see the patients several times, observed. To fix this issue, Baars founded HartKliniek. In the HartKliniek centres, cardiologists are assigned a maximum of 15 patients per day, leaving considerably more room for thorough diagnosis, treatment and taking time to attend to the questions of each individual.

A good doctor must listen

This opens up opportunities to perceive a patient as more than just a collection of medical parameters with a malfunctioning part of their body's machinery. 'In many cases, you have to dig deeper to see where heart problems have their roots,' Menno Baars points out. 'To be a good doctor to your patients, it's essential to listen,' adds cardiologist Bettina Massaar-Hagen. In this regard, HartKliniek just might fill a gap that has been present in cardiac care for far too many years.

The concept of paying more attention to patients especially appears to strike a chord with the female population, the COO notices. Women appreciate doctors who put greater emphasis on communication rather than just performing the required examinations.

Taking this into account, a more precise diagnosis can be established in female patients, since the symptoms caused by cardiac problems can differ greatly between sexes.

It is not rocket science to figure that treating fewer patients in the same time would generate less money. Thus, financing such a concept proved challenging – but the founders came up with a solution: By trimming management layers, medical assistants, nurses, expensive equipment and other redundancies, the centres are able to operate profitably. This means that the cardiologists themselves have to do tasks that are normally delegated to other staff: anamnesis, consulting with the GP or performing the actual examinations. This approach is well-received by the patients, as positive feedback shows. The HartKliniek centres boast top scores in patient satisfaction across the whole Netherlands, Baars states – not a mean feat in an area where many heart patients tend to faithfully stick to their trusted doctor rather than turning to a relative newcomer.

GP, hospital and the HartKliniek makes three

The centre's profile is further sharpened by adhering to low-complexity procedures. Emergency or open-heart operations are not performed. Patients in need of stents, ablation or a bypass are referred to the respective specialists in the surrounding institutions. This is also beneficial for the bigger hospitals as they can concentrate on more severely ill patients without less complex cases burdening their perpetually busy schedules. With this approach, the HartKliniek acts as the missing link between primary care at the GP and highly specialised cardiology departments of hospitals. This interplay between healthcare providers works due to a well-maintained network that aims to assign the patients to the institution that best fits their needs through referrals in both directions.

Chinese-Dutch collaboration in ultrasound

For diagnostic work-up and patient monitoring, the HartKliniek centres rely on ultrasound systems from Mindray. 'Coming a bit from outside ourselves, we wanted to go with a company not yet as well-established in the Netherlands,' says Willem Baars explains. 'After comparing several systems, we decided to equip our centres with M9 portable ultrasound systems from the Chinese manufacturer.'

20 Mindray systems are now installed across the centres. Pivotal features were high resolution displays as well as the capability to configure the devices to perfectly fit cardiologists' requirements. At the HartKliniek centres, the Mindray systems are used for 2-D echocardiography, Doppler exams, carotid IMT measurements and diagnosis of mitral valve abnormalities, says Massaar-Hagen. "We aren't yet doing 3-D echocardiography exams.'

This led to a fruitful partnership between Mindray and HartKliniek; while the patients benefit from the advanced imaging possibilities provided by the Mindray ultrasound systems, the cardiologists give valuable feedback to the company to further gear the systems towards applications needed in the cardiology setting. The digital backbone is a DICOM PACS which serves as a platform for the images generated. The ability to share image data across the HartKliniek centres and with external hospitals enhances the cooperation between the institutions and saves time and money by reducing unnecessary repetition of ultrasound exams.

Menno Baars is founder and CEO of HartKliniek, a chain of specialist medical diagnosis and treatment centers for cardiovascular diseases in the Netherlands. Born in Utrecht, Baars obtained his medical degree at the University of Utrecht and Harvard Medical School in Boston, USA. After gathering practical work experience as a general cardiologist in hospitals during for almost 20 years, he started HartKliniek in 2014. Along his medical expertise, Baars is also an internationally renowned artist with his paintings being displayed in worldwide art exhibitions.

Neurosurgical oncology

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Using contrast helps to obtain anatomical evidence and histology, and also to identify tumour remnants. It then brings visibility of the tumour's feeding artery and draining vessels, the cystic and solid components of the tumour, and other key findings that can be very important information for surgeons. Contrast also helps to obtain some hints about histology about grades of glioma, and, perhaps more importantly, may help to distinguish radiation-triggered necrosis from other cystic lesions. 'With different degree of contrast uptake, you can differentiate between radiation necrosis and other cystic lesions such as metastases and abscesses, because radiation necrosis will never show contrast uptake,' he explained.

Simulation training

In addition, contrast uptake enables identification of tumour remnants, which is useful in the case of doubt about some possible presence of residual tumour. The EFSUMB recently revised its guidelines, introducing the indication for using contrast in ultrasound-guided neuro-oncological surgery procedures to assess tumour boundaries, perfusion patterns and residual tumour. Intraoperative ultrasound has its drawbacks. It is based on unusual imaging and presents orientation difficulties. It also needs specific training and a few solutions have been developed in that sense.

Di Meco and team at C. Besta Institute have developed, within a wider neurosurgical simulation program, a simulator of intraoperative ultrasound for brain tumours. The simulator comes as a software, which, upon pairing their smartphone to their computers, surgeons can rehearse intraoperative US cases just as in the operating room (OR).

'Using a smartphone as a mock US probe and rehearsing intraoperative US scans with co-planar neuronavigation images, surgeons and residents may practice and learn the semeiotics of brain US scans without having the pressure of being in the OR,' he said. This simulator is freely available on https://neurostream.academy/.

There is additional potential for ultrasound in neuro oncological surgery. For instance, high intensity focused ultrasound has been approved already to treat essential tremor, Parkinson's disease and pain. 'You can either use thermal ablation or the capacity to induce blood brain barrier disruption,' Di Meco said. Another interesting development is the use of an US transparent cranial prosthesis that provides a window in the skull for US scans, by replacing the cranial bone flap. 'This can be useful in order to follow-up patients and to disrupt the blood-brain-barrier,' he pointed out.

'US is a polyvalent modality, which encompasses several techniques including Doppler, elastosonography, contrast, blood brain barrier disruption and focused ultrasound – all of them,' he concluded, 'very promising in brain tumour treatment.' (MR)