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.

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 filter, 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.’

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 lab and 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 specificity 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 popula-

tion, 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 and 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.
**Hospitals must think big, small and new**

AI in clinical practice

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 predominate? A panel of European and US experts gave concrete examples of AI’s current implementation in clinical practice and shared tips on how to start working with AI from scratch during the online Healthcare Information and Management Systems Society (HIMSS) Conference.

**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 world 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, 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.

**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 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.

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, LS1 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 cTnI 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 99.6 percentile upper reference limit of 29.0 ng/L at an imprecision of 0.6%, which fits the criteria of the ESC. Algorithms are 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 NSTE-ACS 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 emergency department. It is described 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 0/1 hour rule-in 80.1% positive predictive value (PPV) were...
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 HealthTech Information and Management Systems Society (HIMSS).

**Report: Cynthia E Keen**

5G technology transmission speed is 10 times faster 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 an average of 1-2 milliseconds—critical during interactive communications. In 2013, the European Commission (EC) established a Public-Private Partnership on 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. The 5G PPP is recommended to monitor 5G market developments.

USA telecommunications companies are studying industry 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. Savings: millions of dollars. With HIMSS vice president Stephen Wellman moderating, the roundtable, “Removing Bandwidth Barriers: Impact of 5G in Healthcare,” discussed how 5G might 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 in the 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 Patil, Innovation Consulting Director at Healthbox, a HIMSS solution and healthcare advisory firm. Telehealth, developed for rural areas in the 1990s, 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 the travel challenges great distances several times a day facing 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 include 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 could 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 Venkateshwara 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 5G networks means A&E physicians can receive real-time health status data, and images instantaneous. 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 care to counter stroke symptoms that develop quicker than the time taken to reach hospital. However, only knowledgeable physi- cians should order such dangerous and powerful drugs. Also, if emer- gency 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 net- works at remote testing sites. If a 5G network was available, this would not have been necessary, Donohue said. 5G availability could also enable remote monitoring of patients with exposure to Covid-19.

**Other applications**

These include robotic surgery, augmented and virtual reality applications to simulate surgery for physician train- ing, and home care and remote patient monitoring, such as non-intervention- al blood sample analysis, seizure pre- diction, drug intake and dispensing. The HIMSS experts believe that, as 5G is deployed, the development of smart personal healthcare products and con- sumer apps will evolve.

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**News & Management**

**HIMSS assesses potential values**

Or 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, skills and disciplines in health technology.

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The 5G wireless technology healthcare impact

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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 Transcendence, 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 hospital wing 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 hernia, 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 this will translate into economic benefits.’

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 Münchenladbach-based medical IT manufacturer and developer of software and hardware Reim 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 Reim Medical’s point of view. One special feature is the 4K UHD imaging: Our Operator three monitors are also available in UHD versions and are offered with various display diagonals,’ explained Roland Schliepberg, Key Account Manager at Reim 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, Reim 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 Reim 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. ‘Reim 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 Reim Medical is also responsible for the IT equipment. The additions are to be the renovated and newly equipped operating theatres. ‘In future projects, too, we will work with Reim Medical,’ explained Rolf Rathjen, Head of Medical Technology. ‘We will certainly be happy to return to the specialist knowledge and products of Reim 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€*
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*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.
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 confidence in diagnosis (particularly during the current pandemic). Medical teams frequently use POCT devices to assess acutely ill patients; a hospital’s diagnostic laboratory is responsible for the analyses, 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 Medicine, 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 metabolite 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 et al). Preanalytical quality improvement: from dream to reality. Clinical Chemistry and Laboratory Medicine. 2011;47(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 of 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 errors 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. He says ‘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. With POCT in place, nurses can consider options for 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 delivers results. Therefore, having POCT systems that give reliable results are vital in critical care nursing.

Quality management

POCT devices are preanalytical instruments that fall within the domain of the hospital laboratory management quality. However, they are widely dispersed in many locations in different departments across a hospital. This creates a number of quality assurance and compliance purposes.

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 to work 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.

Clinical staff education

Tintu indicated that, given high staff numbers and turnover, there can be a challenge in maintaining accurate records and knowledge of sample types, 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 POCT results, is another vital laboratory responsibility. This helps to ensure early availability of results and 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 ‘one more’ point on the sample 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 diagnosis and, in some cases, leading to 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 POCT devices that are able to communicate the need to POCT users, he believes further services could be provided. For example, increased satisfaction among those users and ultimately improve patient care. Clearly, different groups of health-care professionals have differing views on what POCT should provide.

* 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 BD Becter (TM) System also allows for the rapid detection of influenza A & B, Group A Strep, RSV and SARS-CoV-2 (US approved).
The clinical potential of POCT

In 2019, the Central Laboratory of the Institute for Clinical Chemistry and Pathobiocchemistry 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.

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...
**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. MAP has 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 unexpected—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 protein and RNA, which can be broken up and visualised in mass spectrometers. From March, MAP Sciences teamed up with Professor Jonathan Henney at Cambridge University to understand the biology of the virus, and developed the biochemical approach for a new MS Covid-19 test. 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 unappealing 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. The spatula, which is then delivered to the lab where ice cold acetone is added to the solution, can 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 viruses 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.

**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 his 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.
Mass spectrometry advances

Since the Covid-19 epidemic took hold, the public has expected ‘unprecedented progress from the scientific community,’ observed Dan Shire, senior vice president and president of the analytical instruments division of Thermo Fisher Scientific. ‘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.’

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 characterization and small-molecules. The Thermo Scientific Orbitrap Exploris 120 mass spectrometer is among the new systems.

Daniela Zimmermann (E1H) asked Deb Bhattcharyya 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 differences 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’s software packages, can offer robust, reliable, reproducible LC-HRAM/MS data for any analyte, regardless of the matrix complexity.’

Could creating an efficient pocket mass spectrometry 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-ICM™ 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 streamlined time-to-result.

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.’

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Cancer development begins within...
Cancer development begins within the genes. Detection during, not between screenings is best. The massive Pan-Cancer Project looks at the activity of 70 genes in them, hence intensive research in the body's immune system to fight and hide. Therefore, 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 “visibility 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 and destroy cancer cells and 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 (BBIG), Professor Peter Studer from the Institute for Informatics, Chair of Bioinformatics, and their teams.

They analysed sequence data of malignant lymphomas, 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 cancer and of its heterogeneity. They have been active in different areas of genome research of cancers for over a decade and are leading in this field internationally. Work arising from the worldwide project will now be continued and centred around clinical implementations.

More personalised screening needed

Women with incident and proliferative benign breast diseases (BBBD) are likely 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**

BBBD, a group of non-carcinous 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 likely to become carcinomas, 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 BBBD diagnosed on their first mammographic screening,” said Dr Marta Roman, a senior researcher in the epidemiology department at the Hospital del Mar Medical Research Institute, during the conference.

**Proliferative BBBD detected from 2nd screening onward linked with higher risk**

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

With their study, just published in a special supplement to The Breast (Differences in breast 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.

Women with prevalent BBBD had a 2.67-fold increased chance of developing breast cancer compared to women with no BBBD, while women with non-proliferative BBBD had a 1.96-fold increased risk.

They found that women with proliferative BBBD had a 3.26-fold increased chance of breast cancer compared to women with no breast disease, while women with non-proliferative BBBD had a 1.96-fold increased risk.

“The highest risk of breast cancer in women with incident, proliferative BBBD. They had a nearly four-fold increased risk of breast cancer compared to women with no BBBD,” Roman said.

Women with an incident, non-proliferative BBBD had a 2.99-fold increased chance of subsequently developing breast cancer compared to women with no BBBD, women with prevalent, non-proliferative BBBD had a 2.85-fold increased risk; and women with prevalent, non-proliferative BBBD 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.

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“High risk

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 DMF rate of 98.2% in 118 women with ultra-low-risk tumours, 93.6% in the 598 women with low-risk tumours, and 93.8% in the 2,388 women with high-risk tumours.

Patients with interval cancers had an eight-year DMF 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 Cardoso 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.’ (MO)

www.healthcare-in-europe.com
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 histopathological 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

The 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 stimuliated 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 later 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 multiple 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.

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.

ISGhigh profile was of 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 Kölzer, Francesca Demichelis, Yari Ciani

GB, Scandinavia, Belgium:

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 understand ing 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 we kept going.”

Malta: Moira Mizzi

Spain: Mielisande Rouger, Eduardo de la Sota

The Netherlands: Madeleine van de Wouw

USA: Cynthia E. Keen, Lisa Chomaf

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The slow return of mobile units

The coronavirus pandemic has had a severe impact on healthcare services but one area 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.

Aboard 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 & 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 distancing, time, theatre access and anaesthetic availability,’ he said. ‘In treatment terms having patients isolate, added time for PPE, cleaning the equipment and requirement for Covid testing, a consequence of social distancing."

In radiology, a large section of the workforce is employed in safety but also in cost efficiency. Hygienic requirements of a mobile lung cancer screening set-up are relatively high, and it is extremely durable, an investment in safety but also in cost efficiency. Everything else needs to be fought for that capacity now. 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. 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 80 lung cancers.

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

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 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.

In lung cancer screening, Hasan Jouni, Business Development Manager, Siemens Healthineers, addressed the session about the role of 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 improving turnaround time.

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 NHS National Delivery Group for Targeted Lung Health Checks, and past member of the NHS Expert Advisory Group on Lung Cancer Screening.

As little assistance as possible – even when transferring from the examination table at the patient’s own pace. This takes the pressure off of medical personnel; letting them concentrate on what’s essential: the examination. Every other need is secondary. If they need to fight for that capacity now, they will.

With our mobile system, patients can perfectly position themselves on the examination table at their own pace. This takes the pressure off of medical personnel; letting them concentrate on what’s essential: the examination. Everything else needs to be just as professional.

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Imagine: 30 radiation sessions reduced to five

To target ionised radiation as precisely as possible, imaging a tumour is vital in radiotherapy planning. Photon-counting 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 Zimmernmann

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 radiations 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 interest of particle therapy deals with the exact recognitions of the Bragg peak, i.e. the point where the energy of the ion beam reaches its peak and then sharply decreases. Since scientists are still uncertain about exactly where the Bragg peak ends in the bone, a comparatively large safety margin is defined around the tumor 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 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.

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 0.01 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 visualized.

Oxygen imaging at 7-Tesla

‘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 parts. The advantage of a 7-T MRI scanner is not only resolution. ‘There is an interdependence of sensitivity and time,’ Ladd added, saying ‘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. ‘With significantly stronger gradient systems, GE Healthcare, however, has developed a 7-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 part of the system was set. ‘In 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 unrealisable before due to the exceedingly high radiation exposure,’ Ladd explained, ‘including new options for visualising the course of a therapy.’

Innovative approaches were further showcased by Professor Mark Ladd 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.

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, he 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.
MRE plus Fib-4 jointly detect liver fibrosis

Rather than using techniques separately, researchers have determined that coupling image-based and serum-based biomarkers results in 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 pathology 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 populations.’ 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 predictive value for clinicians to rule in patients for avoidable risk of liver biopsy.

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.
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 astronomers 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). 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 irreversible 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 travel 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.

Are you considering sending radiologists into space?


Every year experience on board the International Space Station

‘Acute stroke can trigger focal motor deficit insofar 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 arteriopathy remains 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.

‘For children, a leading cause of acute stroke in children is arteriopathy, especially focal cerebral arteriopathy, which causes 50 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 notably the MRI is the first choice modality in these patients, except when they present consciousness disorders. ‘In this case,’ Husson added, ‘we’ll carry out a CT scan with an anesthesiologist 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 when imaging a child with suspicion of stroke in MRI, however following MRI showed renewed occlusion and stroke extension a few hours later.

‘This evolution, and these possible complications, can be explained by the arthiopathy 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 appreciation of 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 images to explore the universe. The agency must therefore handle huge quantities of data, develop autonomous image analysis systems or completely implement remote treatment of such events, creating training programs with expert radiologists.

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 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.

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Immunotherapy, iRecist and complications

IMMUNOTHERAPIES
Unmask tumour cells and induce lymphocytic rich inflammatory infiltrate
Cyostatic

+ Anti PD-1
+ Anti PD-L1
Inflammatory infiltrate

T cell

Tumor volume reduction not always demonstrated – may be increase in tumour volume, unmasking of 'new' lesions or delayed effect

Report: Mark Nicholls

The evolving area of immunotherapi- es in lung cancer and the role of iRecist treatment assessment proto- cols 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 Universities Hospitals Trust, South of England, focused on immunothera- pie, 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 capac- ity the prognosis was significantly worse. Immune checkpoint inhibi- tors 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-1 and PD-L1, 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 treating naive and receiving immunotherapies, with around half having an overall survival of two years.’

Chemo and immunotherapy combinations

Good radiological responses are also being seen with combinations of chemo and immunotherapy, Sayer added. Looking at response assess- ment, he referred to Millar’s criteria from the 1980s with a ‘common language’ to describe radiological effects in clinical trials, WHO guide- lines, and RECIST v1.1, which 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 chemotherapy, the iRecist consens- sus 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 immunothera- py 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 immunotheray 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 progress- ion radiologically, from that point iRecist begins.’

Hyperprogression is an important concept with rapid progressive disease following initiation of immu- notherapy and is associated with poor outcome, he pointed out and also touched on immune-related toxicities and immune-related pneu- monitis. ‘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 malignan- cies,’ 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 con- siderations, with the pandemic hav- ing 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 is not worse, having Covid-19 while being treated with immunothera- pies, and this might be to do with ‘coping up’ the immune-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 immu- notherapy for some time.’

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 those used in radiology and automated information extraction. (MR)
Multiparametric ultrasound: the extent of resection

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 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, cryptorchidism – 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 chromosomal abnormalities, orchidides 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 hypotrophic, 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 epididymal 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 epididemiitis,’ he explained. ‘Cysts, interrup- tion 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 disease affects about 10 per cent of all men and 30 percent of men among fertile couples; but the condition also can be corrected.

Varicoceles are the commonest cause of obstruction in vas deferens and seminal vesicles, which can also be assessed with ultrasound.

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 per cent of all men and 30 percent of men among fertile couples; but the condition also can be corrected.

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New European guidelines for varicoceles

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Evolving role

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‘Varicoceles are the commonest cause of obstruction in vas deferens and seminal vesicles, which can also be assessed with ultrasound.

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

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 Pelvic Imaging Working Group of the European Society of Urogenital Radiology (ESUR-SPFWG) has released guidelines and recommendations on how to perform MP ultrasound for varicoceles. The publication describes 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 size and diameter 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 echochar-acteristics, absence of a kidney. Obstruction in the ejaculatory ducts may be caused by stenosis, stones or cysts, which can also be clearly shown by ultrasound.

Anospermia 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.

Malformation commonly associated with other abnormalities, such as absence of a vas deferens or absence of a kidney. Obstruction in the ejaculatory ducts may be caused by stenosis, stones or cysts, which can also be clearly shown by ultrasound.

Urogenital Radiology (ESUR-

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, intraoperative MRI, fluorescence and intraoperative ultrasound (US). The latter presents patients and benefits during and after surgery, although it remains an unusual imaging tech-
cal sequence to look for wall haemato ma 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 affects 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 cardiac care for the benefit of patients. We spoke with Menno and Willem Baars, members of the founding trio, about the origins of 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, Dronterum, Groningen, Leidschendam, Mijdrecht, 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 profitability. 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 hospitals are reluctant to hire another doctor simply to 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 3D/4D 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 2D/4D echocardiography, Doppler exams, carotid studies, as well as techniques including Doppler and diastolic examinations of mitral valve abnormalities, says Massaar-Hagen. ‘We aren’t yet doing 3D echocardiography.’

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.

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 metasta-

ses 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 EFUMB recently reviewed 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 semantics of brain US scans without having the pressure of being in the OR; he said. This simulator is freely available on https://neuro-stream.academy.

There is additional potential for ultrasound in neuro oncological surgery, well-received by the patients. Di Meco emphasized that ultrasound has been approved already to treat essential tremor, status epilepticus and pain. ‘You can either use thermal ablation or the capacity to induce blood brain barrier disruption,’ he reviewed.

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, elastography, in addition, contrast, blood brain barrier disruption and focused ultrasound therapy can be conducted, ‘very promising in brain tumour treatment.’ (MRI)