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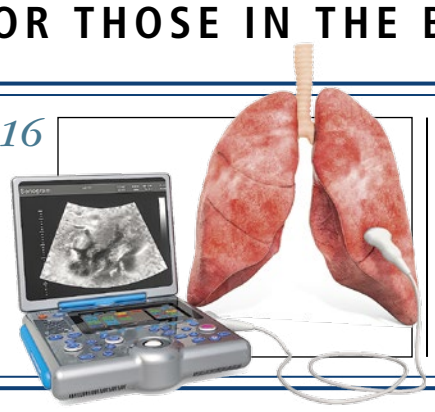


The struggle to create contact-tracing apps

While scientists recently confirmed the crucial role contact-tracing apps play in containing the COVID-19 pandemic, politicians are exploring which app architecture offers better privacy protection. However, there is no doubt that in Western countries such an entirely voluntary app can only be successful if the population at large supports it.

Report: Cornelia Wels-Maug

The emergence of the coronavirus COVID-19 switched a spotlight onto digital health technologies. Most countries tried to contain the virus with a more or less comprehensive set of lockdown measures – now being slowly lifted alongside lowering infection rates. To prevent the infection rates from surging again, many governments are looking into coronavirus contact-tracing apps that could help to disrupt infection chains early on. The study 'Investigation of a COVID-19 outbreak in Germany resulting from a single travel-associated primary case: a case series', recently published in The Lancet, confirms that such an app is a crucial tool to contain the pandemic.

How a contact-tracing app should work

The basic principle of such an app is the exchange of individual identification numbers when people meet, a specific minimum distance is not maintained and a defined period of time is exceeded. The strength of the Bluetooth signal estimates the distance. The app issues a so-called daily tracing key for each user which, in turn, generates a short key several times per hour. If a person tests positive for SARS-CoV-2 he/she must enter this information in the app. All smartphones regularly retrieve a list of anonymised IDs of infected people to determine whether a user was in contact with an infected person. Those affected are asked to test for SARS-CoV-2 and self-isolate, whilst their identity is not revealed.

Experts point out that a coronavirus contact-tracing app is only effective if at least 60 percent of the population use it. This poses the question whether the use of a tracing app should be mandatory or voluntary. Each society will have to decide about this based on its values. Surveys in Germany have shown that about 50-70 percent of the population are prepared to install such a tracing app – if privacy is protected.

Centralised versus decentralised data storage

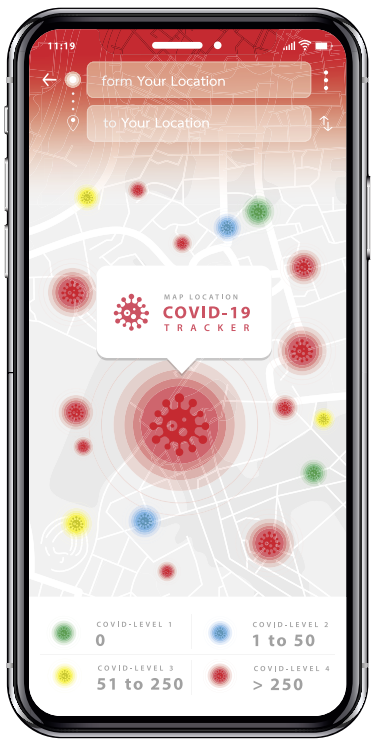
This is a controversial issue. In Germany, the government did an about-face and finally settled on a decentralised data storage architecture after it initially favoured a centralised approach. The same might happen in the UK.

In the centralised storage approach, the server traces with whom an infected person was in contact; in the decentralised approach this task is performed by the individual smartphones.

The Pan-European-Privacy-Preserving Proximity Tracing Consortium (PEPP-PT) supports a centralised approach, which in turn is supposed to be implemented in national tracing apps. However, especially Apple and Google favour a decentralised approach. They plan to jointly develop the basis for a tracing app on a system level, to enable data exchange between their systems and, consequently, between the majority of smartphones. The two tech companies opt for open source and anonymity.

They announced they would make their smartphone programming interfaces for the coronavirus tracing apps available for only one application per country to ensure a homogenous app landscape. Nevertheless, they agree to cooperate with countries that wish to have different apps for different regions.

Apple and Google are not involved in the actual development of the app – this is taken care of by developers in the individual countries. The app will be made available for download via the app stores. There will not be a central database where the IDs of the mobile devices are stored; most data will be stored locally on end users' mobile phones.



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The UK, France and Norway opted inter alia for centralised data storage while Germany, Italy, Switzerland and Austria adopted the decentralised approach.

Country comparisons

China's tracing application is mandatory

When the lockdown was lifted in Wuhan in April a mandatory COVID-19 tracing app was introduced. This is linked to a user's ID and the data is accessed centrally. The app is integrated in the popular messaging app WeChat and in the widely used online payment system AliPay.

The app uses augmented reality (AR) and needs the ability to scan QR codes. Users must provide certain information on their health status. Moreover, the app accesses other information, such as recent travel data, information regarding the social environment and health records. After having processed this data the app issues a colour code to the respective user granting (green) or denying access (red) to certain locations. A yellow respectively red code means one week and respectively two weeks self-isolation. Only those with a green code are allowed to use public transport and enter shopping centres.

Germany, Italy and the UK opt for voluntary cooperation

In late April, the German government asked Deutsche Telekom and SAP to develop a contact-tracing app based on a decentralised data storage concept. On 13 May, a preliminary concept was presented on Github with a roll-out target of mid-June. The app was launched on 16 June under the name 'Corona-Warn-App'. So far, the app has been downloaded 14 million times.

The decision by the German government to abandon their initially favoured PEPP-PT solution was a response to severe criticism by data protection advocates. According to the government, it fully complies with European and German privacy laws. Only epidemiologically relevant contacts in the past three weeks should be stored on the users' smartphones in anonymised form. Movement profile will not be stored and the use of the app is voluntary.

'Immuni' is the Italian version of the coronavirus contact-tracing app developed by Bending Spoons S.p.a. Its use is voluntary, and users will maintain control over their data. Only when a person tests positive for SARS-CoV-2 will the data be transmitted to a server. All recent contacts will be identified via Bluetooth and alerted. According to Bending Spoons, the app, which was launched 8 June, complies with European privacy laws. The company granted the Italian government rights of use and future updates free of charge.

UK follows a two-pronged approach

Originally, the British government opted for a centralised data storage architecture with users uploading their data to a central government server as soon as they develop corona symptoms.

A test version of this app is available in the app stores and has been tested since 5 May on the Isle of Wight. If the test results are satisfactory the app will be rolled out UK-wide. However, there is a discussion as to what will happen with the data post-pandemic. Matthew Gould, CEO of NHSX – the digital innovation arm of the English National Health Service (NHS) – explained that the NHS will use the data only with the data owner's consent and will be stored a maximum of 28 days.

In the meantime, however, technical and ethical concerns were raised within the government and a second app with a decentralised architecture is being developed just in case the first app turns out to be not supportable. So far the NHS has not committed to a timeline on when the app will be launched.

Upon publication of the article in Lancet, Professor Annelies Wilder-Smith of the London School of Hygiene & Tropical Medicine publicly emphasised the significance of a contact-tracing app. 'All countries that have introduced rigorous contact tracing were most effective in keeping the number of newly infected people small. South Korea, Taiwan, Hong Kong, Thailand, Vietnam and Singapore are clear examples of countries that do not economise on resources and technology to carry out rigorous contact tracing.' Hopefully, the app will be rolled out soon and using international standards so that it can support all users once travel restrictions are lifted.

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A united strategy counters COVID-19 spread

Corona control in Taiwan

Despite its proximity to China, Taiwan contained COVID-19 successfully, without a lockdown or movement restriction measures introduced elsewhere. With few new cases reported, life almost returned to normal. Behind the scenes, however, efforts have continued to maintain that positive situation. The medical directors of Taipei Medical University Hospital (TMUH), a 727-bed facility in the Taiwanese capital, have explained how the coronavirus affects clinical workflows.

Report: Wolfgang Behrends

'In our hospital, COVID-19 has entirely upended daily routine,' said hospital superintendent Dr Ray-Jade Chen. In fact, protection measures set in before you even enter the building: all visitors' entrances – except one – are closed. Whoever wishes to enter the hospital has to undergo a multi-step control procedure at the one remaining open door. Since fever is one of the major COVID-19 symptoms, body temperature is taken via infrared detector; in addition, the so-called TOCC check collects information on travel, profession and contacts.

Due to the sophisticated digital infrastructure in Taiwan's health system, most of the necessary data is quickly scanned from the electronic patient card every citizen holds.

With the exception of corona treatment, clinical procedures are reduced to a bare minimum. Elective interventions are currently not offered as distancing of patients is strictly enforced. To reduce waiting times inside the hospital, and thus the risk of hospital-acquired infections, all patients are reminded of their appointments by push messaging on their smartphones.

When in doubt, isolate

The hospital aims to beat the infection risk with strict prevention measures, Dr Chen explained. 'Any patient who presents with fever or respiratory stress symptoms is considered a potential Covid-19 patient.' This policy, according to the superintendent, is key to Taiwan's success in beating the virus. And indeed, the island has recorded very low case numbers and COVID fatality rate compared to its neighbours.

To keep the COVID-19 pandemic in check, doctors and staff at TMUH face the challenges as an indivisible unit

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As far as diagnosis is concerned, TMUH uses RT-PCR tests (reverse transcription polymerase chain reaction), said Dr Li-Yuan Chen, infection expert at the hospital. 'This technique offers high specificity and is thus well suited to distinguish COVID-19 infections from other pathologies with similar symptoms.' When PCR test results are unclear, a CT scan is indicated. CT furthermore is used for follow-up.

Patients with suspected infection are moved to a dedicated ward with the availability of quarantine beds

being a major aspect of the anti-corona strategy, said TMUH head pulmonologist Dr Pai-Chien Chou. For additional hospital staff protection, COVID-19 patients are separated according to the disease severity.

First line treatment is the malaria drug hydroxychloroquine, which has yielded promising results in various studies due to its anti-inflammatory properties and ability to reduce virus proliferation. In severe cases, treatment is supplemented by the HIV drug lopinavir, the macrolide antibiotic azithromycin und interferon beta.

A strictly enforced strategy and diligence pay off

To minimise infection risk, TMUH management designed an elaborate system of work areas and routes to avoid unnecessary contact: the paths of lab staff, radiologists and nurses do not cross and supplies marked for disposal or decontamination are beelined along dedicated corridors. Before staff are in contact with COVID-19 patients they undergo a minutely monitored procedure with more than a dozen steps. This diligence pays off. 'To date, we have not seen a single infection among our staff,' superintendent Chen proudly reported. 'Should a member of our staff contract the virus despite the protection measures, we are well prepared to prevent the virus from spreading throughout the hospital,' infection expert Dr Chen added.

'Fortunately, the infection rate in Taiwan is very low,' said Dr Po-Li Wei, deputy superintendent. 'This is, to a large extent, due to our government taking containment measures very early.' After the SARS epidemic in 2003, the Taiwanese government established the National Health Command Centre (NHCC), a central institution which has also led the efforts during the current pandemic.

To avoid bottlenecks, the NHCC inter alia coordinates the production and distribution of personal protective equipment. Digital tracking allows quick identification and warning of contacted people before a spread of infection.

In addition to diagnosis and therapy, the third pillar in the strategy against the virus, Dr Chen said, is information. 'As a hospital, we carry an immense responsibility and we face the challenge as one indivisible unit. Thus, we not only train our clinical staff with regard to disinfection best practices, donning or taking off protective equipment or handling patients. All our employees, from technician to cleaning staff, receive in-depth training on protection measures.'

'Our employees are worried since many questions regarding the virus remain unanswered. We take these concerns seriously and ensure that all are up-to-date and feel well protected,' he emphasised. 'This is the only way for us to ensure that we can reliably perform our duties towards the people.' Taiwan, he added, learnt many lessons from the SARS epidemic almost 20 years ago.

'At this point, nobody can tell for how long this emergency situation will last,' he pointed out. It is also important to look at other countries to gain a complete picture of developments. 'People around the globe are working hard to develop drugs or vaccines against coronavirus and COVID-19. This global sense of community has triggered many research cooperation projects and a fruitful exchange of ideas across borders. We are convinced that this is the right approach. Together we will find a way out of this pandemic.'

To ensure patient and staff safety, TMUH management implemented extensive measures for infection control

* This year's Medical Taiwan international medical, health and care expo (15-17 October) will follow a conspicuous theme – epidemic prevention – within which diagnosis, therapy and prevention of the COVID-19 will be a focus topic.

Public acceptance of electronic health on the rise

Focused on updating healthcare through digitisation, 41 experts and around 500 delegates gathered for the 4th 'Digital Health Conference' late in 2019. At the Berlin venue, they focused on solutions such as the potential lack of skilled staff, demographic changes, urbanisation and multimorbidity.

The organiser, Bitkom, the German digital association which represents more than 2,600 communications companies, had also organised a representative survey of the country's general public, with results that reflect the positive attitude towards digital offerings in healthcare across all age groups.

Of the 1,005 people surveyed, 65% stated they would utilise the electronic health file; 63% confirmed that they would use electronic prescriptions and 30% stated that they would be happy to discuss their symptoms with their family doctor during online appointments, instead of visiting the surgery. That level of acceptance is an important prerequisite for the modernisation of the healthcare system.

Digitisation as a political mandate

In his keynote speech, Jens Spahn, Federal Minister of Health, stated that he was 'accelerating digitisation' to create 'comprehensive and efficient healthcare'. It is hoped that digitisation will also 'maintain and win back the trust' which the German public had lost over the debacle around the electronic health card, which the Federal Minister of Health referred to as the healthcare equivalent of the saga swirling around the new Berlin Airport'.

Spahn also appealed to doctors to accept the need for obligatory connection to the telematics infrastructure, which should make day-to-day communication with patients easier.

Furthermore, the Minister urged for the utilisation of the innovation potential inherent in digitisation and not to limit discussions only to data protection and data sovereignty.

To this extent, Spahn called for an active, balanced debate to ascertain exactly how technology can benefit medical staff as well as improve healthcare.

Suggestions for the modernisation of the healthcare system

Which solutions look particularly promising? Digitisation is a means to an end to achieve better medical care, confirmed Dr Barbara Holtz, Expert Business Consultant at Dassault Systèmes, but also queried 'What does better look like?' Some examples of successful digitally supported offerings were introduced at the conference.

Thomas Friese, SVP Digital Platform at Siemens Healthineers, explained the potential of clinical decision-making support systems when imaging procedures are needed for diagnoses. This is particularly important, given that a survey showed 26% of image studies in the USA do not correspond with the diagnosis because the doctors do not quite come to correct conclusions from the patients' information.

Holtz spoke of the development of personalised therapies, using the concept of a digital twin, and about apps for data acquisition. Using this data, the industry wants to model possible effects of, and reactions to, medication to help improve processes and exclude risks in advance. This concept is based on the automotive industry where the first five models of a production line are routinely crashed to achieve better products more quickly and to save costs.

Holger Müller, Business Solutions Architect at Cisco Systems, explained

"A patient's home has to become a mobile diagnostic centre"

Video consultations are rising

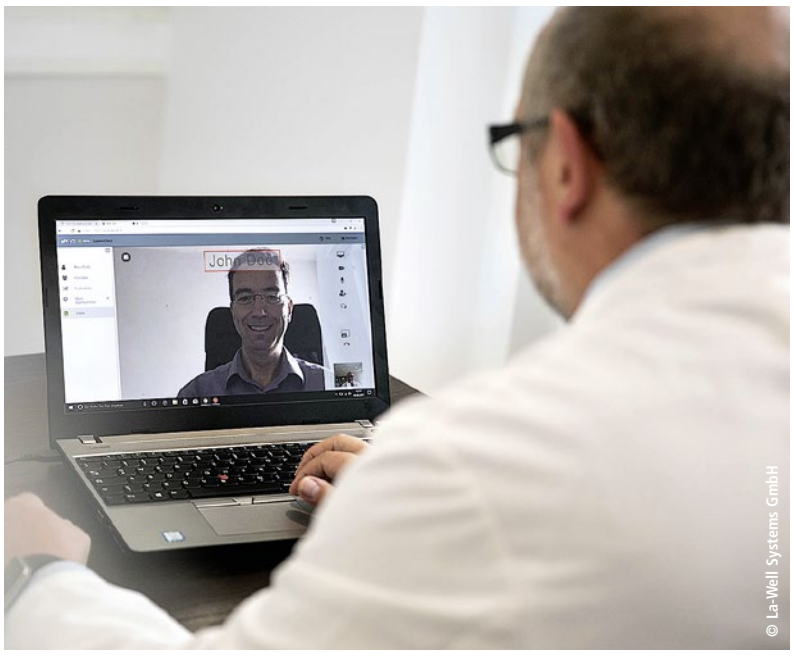
Report: Sonja Buske

There are many reasons why for some patients a visit to the doctor's office is difficult or well-nigh impossible – limited mobility after surgery, old age, or a handicap. For others, particularly in rural areas, the doctor is often far away and/or difficult to reach due to poor public transport. In times of corona, another import ant issue emerged: infection protection. In such cases, video consultation can become a vital safety net.

More video consultation since COVID-19

The Centre for Telematics and Telemedicine (Zentrum für Telematik und Telemedizin – ZTG), co-funded by the German state of North Rhine-Westphalia, helps physicians and healthcare institutions with video consultations, from general information to selecting a suitable, certified system and to help with technical and organisational issues. 'The future belongs to video consultation,' confirms ZTG managing director Rainer Beckers. 'Before corona, online consultations were hardly ever used, even though they've been a billable service for years. Since Covid-19, that has changed significantly.'

Daily, ZTG is receiving inquiries from all over Germany – and ZTG team members are happy to help. As of 20 May 2020, the National Association of Statutory Health Insurance Physicians (Kassenärztliche Bundesvereinigung – KBV) listed 31 certified providers of video consultation software systems. Clickdoc, a solution developed by CompuGroup Medical SE (CGM), reports 80,000 users worldwide and more than 33,000 in Germany. According to Dr Ralph Körfgen, member of the CGM board and responsible for health information systems, CGM is one of the leading providers of online healthcare consultation systems in Germany. Since March, the company provided its system free of charge during the corona pandemic to office-based physicians, hospitals, midwives and social service institutions.



Conferring in a patient/doctor video consultation

In 2016/17, an international standard for combined video and audio broadcasts via browser was adopted, i.e. audio and video conferences can now be held without additional software. Before this standard was implemented, patients were allowed to call the doctor but not send personal data by mail, or make a video call. 'State-of-the-art encryption technologies comply with very high security standards, which ensure privacy protection,' Beckers points out.

A simple procedure

The procedure is very simple: doctor and patient agree a date and time for an online consultation. The patient receives a code to initiate the video call via desktop, tablet or even smartphone. A dedicated software package is not necessary. The patient is directed to a virtual waiting room and 'called in' by the doctor.

Abusing the system is virtually impossible, since the participants see each other and in most cases know each other. Patients who visit the doctor for the first time must identify themselves with an electronic health card.

Obviously, a video consultation has its limits. When a physical exam is needed, e.g. to differentiate bronchitis from pneumonia, the patient has no choice but to visit the doctor's office. While online consultation is possible, online auscultation is still pie in the sky. 'It is the doctor's responsibility to make this decision,' Beckers explains. 'For many other diseases and problems, such as evaluation of wounds or eczema, or follow-up exams after surgery, video consultation is perfectly well-suited. Transferring documents or X-ray images is no problem either.'

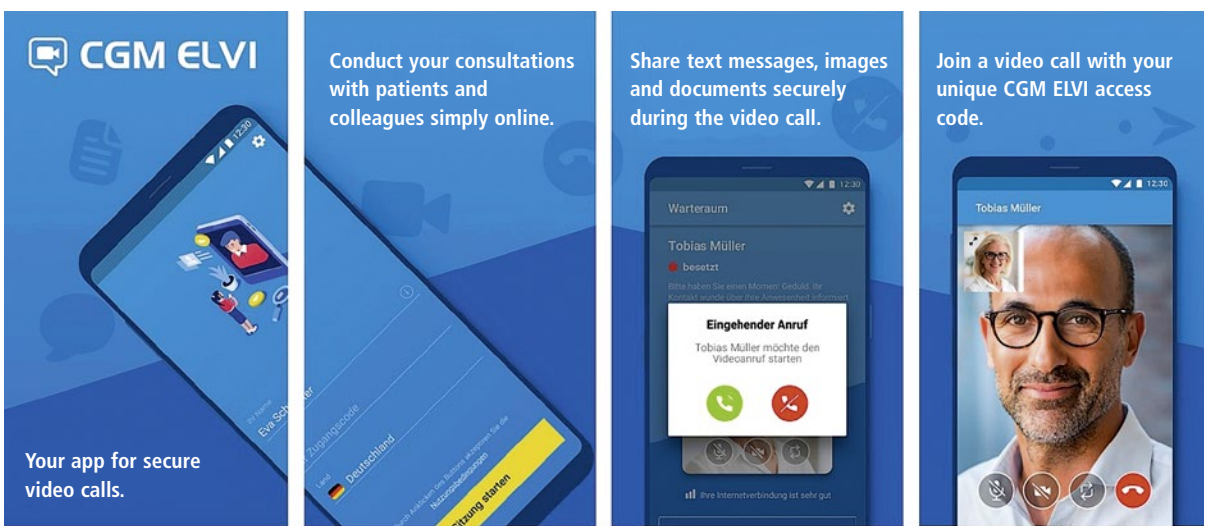
A look into the future

Indeed, auscultation per video call, Beckers says, is not as utopian as it might sound: 'The home environment has to become a mobile diagnostic centre. That means that the video consultation has to be complemented by tele-monitoring.' Smart blood pressure measuring devices or mobile ultrasound systems will enable the physician to collect the patient's vital data. 'It's a matter of the type of equipment the patient has at home,' says Beckers and adds confidently that 'the future belongs to video consultation combined with tele-monitoring!

Health scientist and philosopher **Rainer Beckers** currently focuses on health economics and computer simulation as a scientific method. He has worked within healthcare since 1989, in research, hospital management and in professional healthcare associations. Early on, Beckers was involved in designing the electronic patient record. In 2000, he joined the then newly founded ZTG Zentrum für Telematik und Telemedizin GmbH, and has been its managing director since April 2009. Beckers has also been a long-time member of the board of the Deutsche Gesellschaft für Telemedizin (DGTelemed e. V. / German Society for Telemedicine).

Telemedicine: What's next

- **July 23-24, 2020, Rome:** International Conference on Systems in Telemedicine (ICST)
- **September 23-24, 2020, Vancouver:** International Conference on Telemedicine and Bioinformatics (ICTB)
- **September 24-25, 2020, London:** International Conference on Telemedicine and Clinical Practices (ICTCP)
- **October 29-30, Paris:** International Conference on Biomedical Engineering and Telehealth (ICBET)



care via digitisation

that knowledge around IT security is not yet comprehensive enough: whilst around 90 – 95% of the IT budget is invested in 'block and protect' concepts, not enough funds are pooled into solutions as to what should be done once a security issue has occurred. Müller pointed out the necessity of a 'data lost prevention strategy' as not all data needs to be protected in the same way.

He also emphasised the importance of an application lifecycle policy, because it provides a continuous audit which verifies, in real time, that an application behaves according to its original certification, to ensure that it can be detected at once when an application causes traffic which it did not use to cause.

James Fischer MD, of Roche Diabetes Care Germany, talked about the big advantages for diabetics resulting from the use of a digital diary over a manual diary, using the mySugr App as an example. 'Diabetes is a data management disease,' explained Fischer. Optimum glucose level management for patients requires the acquisition of data, specifically for carbohydrates and other foods consumed, and for sleep duration. Studies have shown that the use of the mySugr App can lower the blood sugar levels by an average of 10.4 percentage points.

Technology is only one aspect of modernisation – there's also 'digital values and digital humanism'

Professor Jörg Debatin, who is Chairman of the Health Innovation Hub at the Federal Ministry of Health, summed up that digitisation should be perceived to be going well beyond purely technological innovations. Digitisation of healthcare requires acceptance, as well as digital values and digital humanism.

It also requires comprehensive training in the use of anonymised data and transparency with regards to the values on which the algorithms are based. By the time we achieve this, several updates will have been carried out already. (CWM)

Jens Spahn, Federal Minister of Health, appealed to doctors to accept the need for obligatory connection to the telematics infrastructure

Catching up with COVID-19

Rapid response test kits – the race is fierce

To develop and manufacture COVID-19 test kits in massive quantities was not part of their 2020 business plans. Yet, as the epidemic evolved into a global pandemic, the urgent need for diagnostic and antibody SARS-CoV-19 test kits triggered an unprecedented scramble among medical manufacturers.

Report: Cynthia E Keen

That urgency in most countries precluded the established procedures required for regulatory approval for their use. When those developed by the U.S. Centers for Disease Control and Prevention (CDC) proved unreliable, the USA's FDA invoked emergency use authorisation (EUA) to allow the use of COVID-19 test kits.

The World Health Organisation (WHO), the European Centre for Disease Prevention and Control (ECDC), and the CDC recommend use of molecular tests, the reverse transcription polymerase chain reaction (RT-PCR) tests, which detect the SARS-CoV-2 virus ribonucleic acid (RNA). These tests need well-equipped laboratories, highly skilled technologists, and multiple reagents. At best, results take about four hours to come and results can take days, if samples are sent to offsite labs.

Reliable rapid diagnostic tests that are relatively simple to perform and interpret and provide results in less than an hour, are vital. The two types of COVID-19 rapid tests include direct SARS-CoV-2 antigen detection and indirect antibody detection. Linda Carter PhD, an information scientist at the American Chemical Society CAS division, explains, in her article in ACS Central Science, that these assays detect viral antigens and are complimentary to molecular genetic assays. The serology tests detect antibodies to the virus in the bloodstream.

Clinical testing and quantified benefits of rapid COVID-19 diagnostic tests

On 1st April, ECDC, in a technical report, warned that even for compliant CE-marked rapid diagnostic tests, performance may vary in the routine testing laboratory compared with a manufacturer's performance study done for CE-marking purposes. ECDC cautioned: 'rapid tests may be less accurate and less sensitive than laboratory-performed diagnostic tests' and that clinical validation of the diagnostic performance of rapid tests for COVID-19 in real life should be carried out by comparing them with standard RT-PCR laboratory tests.

Example: In the UK, in one rapid turnaround laboratory testing device, the SAMBA II, a compact, portable machine developed by Cambridge Uni spin-off Diagnostics for the Real World, after swabs with samples are loaded, the device searches for tiny traces of virus genetic code.

Addenbrooke's Hospital of the Cambridge University Hospitals NHS Foundation Trust, was the first to use the device in a clinical setting. The results of a clinical study of 149 symptomatic individuals showed that SAMBA II had a 96.9% sensitivity and a 99.1% specificity, compared to the standard RT-PCR lab tests.

A subsequent hospital-based implementation study included an analysis of 992 tests of 913 symptomatic individuals over a 10-day period. Professor Ravi Gupta and researchers at the Cambridge Institute of Therapeutic Immunology and Infectious Diseases, reported in medRxiv that the tests were used mainly for emergency department patients, as well as those in the acute admission ward, presurgical patients, and the elderly being discharged to nursing homes.

The median time to a result was 3.6 hours compared to over 21 hours for the standard lab RT-PCR test. The average time that patients had to spend in a COVID-19 'holding ward' before discharge or progress with treatment dropped from 58.5 hours to 30 hours. Use of single-occupancy isolation rooms also decreased, from 30.8% to 21.2%. The research team advised that the switch by Addenbrooke's to rapid testing kept more surgical bays open for uninfected patients and prevented 11 ward closures for these patients in the 10 days after hospital-wide implementation.

Linda Carter PhD, is an information scientist at the American Chemical Society CAS division.

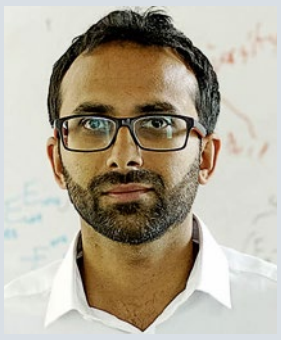
Rapid result COVID-19 antibody tests

Companies responded in droves to develop rapid response antibody detection tests.

Roche, for example, worked 24/7 in late March and April to develop one. In early May, the company announced that its new Elecys Anti-SARS-CoV-2 antibody, approved for EUA use by the FDA and with CE-IVD marking, started shipping worldwide.

Roche reports ramping up production capacity to high double-digit millions per month.

The serology test has a 99.81% specificity and 100% sensitivity in detecting antibodies in blood samples taken 14 days after a PCR-confirmed coronavirus infection, according to results of nearly 5,300 samples. When processed on Roche's Cobas e analysers, results come in 18 minutes, with a test throughput of up to 300 tests/hour.



Professor Ravi Gupta is a researcher t the Cambridge Institute of Therapeutic Immunology and Infectious Diseases

Siemens Healthineers rapidly developed a molecular PCR Fast-Track Diagnostics SARS-CoV-2 Assay test kit to identify antibodies. This molecular test analyses nasal/throat swabs, detects antibodies believed to neutralise the COVID-19 virus, specifically targeting antibodies that attach to a spike protein on the surface of the virus (* CE Mark received April; FDA EUA approval, May).

Rapid results take up to 10 minutes when used with Siemens high throughput immunoassay analysers, which can deliver up to 440 tests/hour, and in 18 minutes with other Siemens analysers that test up to 240 samples/hour. Tests conducted on over 1,850 samples demonstrated a 100% sensitivity and 99.8% specificity.

Siemens is ramping up production to a capacity exceeding 50 million tests per month, starting in June.

Beckman Coulter expects to report the availability of its Access SARS-CoV-2 IgG serology test in June, and plans to produce 30 million tests per month. Hospitals using the company's highest performance immunoassay analysers will process up to 200 results per analyser per hour. Abbott, Cellex, Chembio Diagnostics, and Ortho Clinical Diagnostics have also developed tests.

Potential and perils in home test kits

Home testing kits for initial risk assessment of diabetes, high cholesterol, and colon cancer offer a more affordable and convenient option than on-site diagnostic laboratory testing. Inexpensive, patient-administered COVID-19 testing kits to diagnose coronavirus, or identify the presence of antibodies, could significantly expand population testing.

Need for hundreds of millions of such kits results in academic researchers and companies scrambling to develop them.

RUCDR Infinite Biologics, part of the Rutgers University Human Genetics Institute of New Jersey, developed the first saliva self-collection test to receive a FDA EUA. Everlywell also received an EUA for a self-collection test that utilises nasal swabs to collect a sample. With both, samples go to a lab for processing.

These tests are not without risk. In early April, *The Guardian* reported that 17.5 million coronavirus antibody detection home test kits purchased by the British government had a low sensitivity and accuracy level, according to an unnamed testing expert. The *New York Times* reported that the test kits purchased from two Chinese companies, Hangishou AllTest Biotech and Wondfo Biotech, had been found 'insufficiently accurate by an Oxford University laboratory'. The test kits are not used.

Dr Carter warns that users of home COVID-19 test kits could incorrectly collect a sample, or not place a sample properly in its collection medium, or return the sample late, or the manufacturer has not ensured test results will be reliable under a wide variety of conditions, or that all recipient labs can process samples accurately.

Research continues to develop robust, easy to use, inexpensive tests. With her team, Marit Nilsen-Hamilton PhD, a professor of biochemistry, biophysics, and molecular biology at Iowa State University, is aiming to develop a smartphone size viral testing platform, to identify a DNA aptamer, a nucleic acid that behaves like antibodies in the immune system, which could recognise the viral cause of COVID-19, for diagnosis and antibody recognition.

Nilsen-Hamilton told *European Hospital* that at least a year of research is needed. 'Our long-term vision is to develop a small/portable point-of-care unit that can simultaneously detect several viruses.

The unit would accept a range of chips, each chip containing aptamers that recognise a series of viruses that present clinically with similar symptoms.

With this kind of inexpensive, easy-to-use device, we hope that individuals who are infected with a virus and need isolation, can be rapidly identified, and that a future pandemic such as COVID-19 could be rapidly suppressed.'

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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.....**289€***
ATEM Mini Pro.....**569€***
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Is home sanitisation vital? How long can a virus survive?

COVID-19: Lifespan and disinfection – the reality

Professor Eike Steinmann has been head of the Department of Molecular & Medical Virology at the Ruhr University Bochum since 2018. After completing his degree in biology at Hanover University and Northeastern University, Boston, USA, he completed his doctorate at the Institute of Molecular Virology at Heidelberg University. Steinmann then became a research associate and junior group leader in the Department of Experimental Virology at TWINCORE - the Centre for Experimental and Clinical Infection Research in Hanover. In 2012, he wrote his habilitation in Experimental Virology at Hanover Medical School, and from 2014 he managed the working group on 'Virus Transmission' at TWINCORE. In 2016, he was appointed 'Adjunct Professor' at Hanover Medical School.

Surface disinfection has proved an effective method to control COVID-19 infection, as virologists from the Ruhr University Bochum (RUB) have shown. However, an effective disinfection strategy against Coronavirus must consider various factors, says Professor Eike Steinmann. The head of the Department of Molecular and Medical Virology at the RUB explained when disinfection is an effective procedure against SARS-CoV-2, which agents are suitable to inactivate the virus and why private individuals should not reach for the 'strong stuff' without good reason.

Whether or not a disinfectant is effective against a certain type of virus depends, among other reasons, on the structure of the virus, Steinmann explains: 'Coronavirus is covered by a lipid membrane which stores proteins. This makes it susceptible to alcohol-based disinfectants because they destroy the membrane and inactivate the virus.' If this membrane is missing, as, for instance, is the case with norovirus, other agents need to be used for disinfection.

The use of UV radiation has proved effective against such non-enveloped types of virus because it attacks the nucleic acids (RNA) of the virus. In concrete terms, this means that agents classed as having a limited virucidal effect are perfectly adequate for the inactivation of Coronavirus SARS-CoV-2. However, as more resistant agents, such as the aforementioned norovirus, are also present in a clinical environment, the use of more potent agents (classed as 'virucidal' or 'limited virucidal plus') may also be of benefit.

Effective disinfection should be carried out on all surfaces which have potential contact with the virus: work surfaces and surfaces close to patients, beds, and medical equipment. Current studies on SARS-CoV-2 confirm the presence of the virus – or at least its RNA – in many locations in a room where an infected patient had been accommodated: the edges of the bed, light switches, door handles, but also toilet seats, remote controls and pillows. 'This shows that the virus is spread almost everywhere in the room via contact with hands as well as through the smallest droplets,' Steinmann says. 'However, thorough cleaning and disinfection can reliably deactivate the virus.'

Laboratory lifespan of SARS-CoV-2 gives indications

One of the central issues which researchers worldwide are examining concerns the lifespan of the new coronavirus on surfaces. Whilst initial calculations are mainly based on experience with the related virus types SARS-CoV and MERS-CoV, newer studies provide reliable figures on COVID-19 pathogen SARS-CoV-2: 'One study, published in the New England Journal of Medicine, is of particular interest,' says Steinmann. 'US researchers examined for how long the virus survived on different materials, including copper, carton, steel and plastic surfaces.

The results showed that in some cases, the virus is still present and active after several days. Everyday items such as banknotes, handkerchiefs and masks were tested in another study published in the Lancet Microbe: 'The virus was still present on the inside of masks after 7 days,' says the virologist and adds: 'Although these measurements were taken under laboratory conditions, they give us a pretty good idea of how long the virus can remain stable in everyday conditions.'

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What role does temperature play?

Currently, researchers at the RUB under Junior Professor Dr Stephanie Pfänder are examining the effect of changes in room temperature on the lifespan of the virus. Scientists compared the surface stability of the virus at room temperatures of 4°C and 30°C. They found that the virus remains infectious on surfaces for roughly the same length of time in both hot and cold conditions. 'The assumption had been that higher temperatures would lead to a lower transmission rate of SARS-CoV-2 in summer,' says Pfänder.' However, it appears that the stability of the virus on surfaces is not impacted by changes in temperature.' A potentially lower rate of infection in summer could be due to other factors such as UV radiation and humidity though, says the virologist.

Less is more in private households

Steinmann emphasises that there should be different criteria for private households as opposed to hospitals: 'In everyday life, normal hand washing – combined with social distancing and following the correct etiquette when coughing – is usually completely sufficient. Disinfection is only required once there has actually been contact with an infected person.' Steinmann explains, in terms of the explosive demand for disinfectants amongst private individuals as follows: 'In many cases, this will have been impacted by a psychological effect: If you have a disinfectant at home, it makes you feel safe just in case. The actual use is then not actually that important.'

If private households reach for the 'strong stuff', i.e. a disinfectant – they may not be doing themselves a favour, warns the expert: 'These agents are aggressive and can attack the skin if used regularly.' Without comprehensive care, this can easily result in skin injuries. (WB)

Dr Bill Rutala is the Director and co-founder of the Statewide Program for Infection Control and Epidemiology and a Professor for the Division of Infectious Diseases at the University of North Carolina's School of Medicine. He directed the Hospital Epidemiology, Occupational Health and Safety Program at the University of North Carolina Hospitals for 38 years, retiring in 2017. Also a retired Colonel with the US Army Reserve, and certified in infection control, Rutala is a member of various committees on the local, state, national and international level, plus professional societies that include the American Society for Microbiology, Association for Professionals in Infection Control and Epidemiology and the Society of Healthcare Epidemiology of America.

Study

Confirmed: Steam ster

A new study from the USA highlights how low temperature sterilisation can jeopardise effective cleansing of medical tools and lead to transmission of dangerous bacteria to patients. Steam sterilisation was shown to be the most effective and robust sterilisation technology.

Report: Mark Nicholls

However, the researchers, working at the University of North Carolina, also showed that vaporised hydrogen peroxide (VHP) failed to completely sterilise surgical tools 76% of the time.

Led by Dr Bill Rutala, Director and co-founder of the Statewide Program for Infection Control and Epidemiology, the team simulated the impact of proteins and salts left on surgical tools prior to sterilisation to test the effectiveness of three low-temperature technologies, increasingly required for plastic tools, compared to steam sterilisation.

'Not all sterilisation technologies used in healthcare to sterilise surgical instruments are equal,' Rutala pointed out. 'While sterilisation technology is intended to kill a very large number of microorganisms on instruments, healthcare personnel can unintentionally impede the effectiveness of sterilisation technology by improper cleaning of the instruments prior to sterilisation.'

Cleaning, or the removal of visible soil and microbial contaminants from objects, must precede sterilisation:

'If instruments are not properly cleaned prior to sterilisation and then placed in a low-temperature sterilisation technology such as VHP, there is a possibility of failure,' Rutala added.

He stressed, however, that the robustness of technology, such as steam sterilisation, makes it extremely unlikely that a sterilised instrument will be the source of infection and that most medical and surgical devices used in healthcare facilities are made of heat stable materials and thus are sterilised by heat, primarily steam sterilisation.

Comparison of the microbiocidal activity of FDA-cleared technologies

In their experiments to compare the microbicidal activity of FDA-cleared, low-temperature sterilisation technologies to steam sterilisation in the presence of salt and serum – simulating inadequate cleaning of instruments prior to sterilisation – the equipment was then sterilised with VHP, ethylene oxide (EO), hydrogen peroxide gas plasma (HPGP), or steam.

'This study evaluates the "robustness" of sterilisation technology that is used by hospitals throughout the United States,' Rutala poinred out. 'Robustness is defined as the ability to withstand and overcome adverse conditions or rigorous testing.'

He emphasised that the intention was not to compare the factors that affect sterilisation, such as temperature, duration of cycle, concentration of gas/vapour, but to simply determine whether FDA-cleared sterilisation technologies have the same robustness or "margin of safety".

'Using the methodology defined, we found some sterilisation technologies were more robust than others,' he added.

Steam, EO and HPGP sterilisation techniques were capable of inactivating the test organisms on stain-

Specialty: powerful, essential and valued cleansing systems

Pre-cleaning complex robotic instruments

'We are a medium-size German company specialising in ultrasonic equipment for cleaning, including pre-cleaning of medical instruments from different medical fields,' explained Florian Knuth, Sales Director for the Medical Division of the firm Bandelin, during an interview with *Ralf Mateblowski, of European Hospital*

'We've produced and distributed different types of ultrasonic equipment for pre-cleaning of medical instruments for a number of decades,' Knuth added. 'This ranges from one litre devices for smaller medical practices to large, built-in devices for the Central Sterile Services Department (CSSD). Additionally, we offer specialist devices, such as those required for MIS instruments or robotic instruments.'

Asked about the development and more general use of robot-assisted surgery, Knuth said the advantages are obvious. 'More precision for complex interventions and therefore a clear reduction in the number of surgical errors. However, these high-tech instruments with long lumen, various control wires, detailed cutting tools and complex design also require special handling. The manufacturer supplies detailed instructions for manual pre-cleaning. This involves rinsing, brushing, and moving the instruments in many individual steps. This procedure is very time-consuming.

Knuth: 'Increasingly complex surgical instruments require innovative technical solutions for adequate preparation. Our focus is on achieving optimum safety during preparation using validated procedures, whilst simultaneously saving resources.

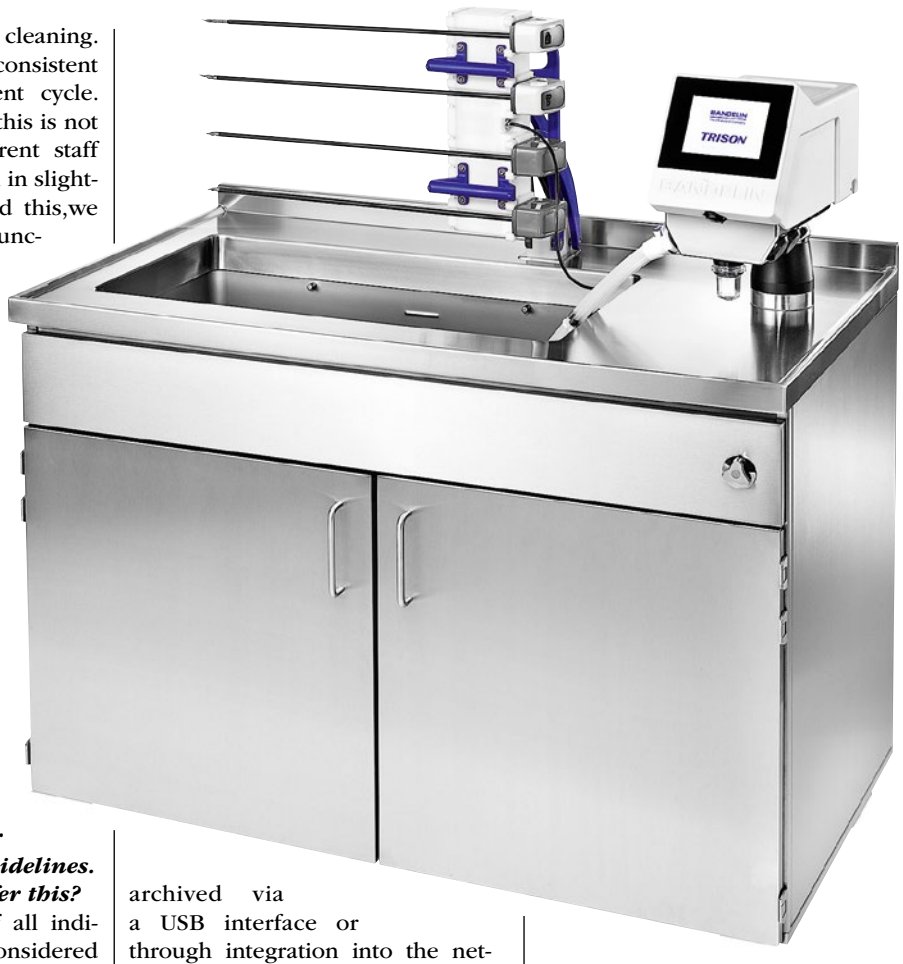
'Our TRISON 4000 ultrasonic bath offers a pre-cleaning procedure which can prepare four highly complex robotic instruments simultaneously, with patented technology. The instruments are treated with ultrasound while being rinsed and moved. Achieving all this in just one single step is unique and facilitates the best possible results in cleaning.

'The system ensures a consistent process for each treatment cycle. With manual pre-cleaning this is not always the case, as different staff members will usually work in slightly different ways. To avoid this,we have integrated a control function, which monitors the device components and correct procedure throughout the process. We have also integrated a rinse control function, meaning that, should one or several instruments still be blocked after treatment, this is indicated on a large display. This function provides additional security to ensure the correct condition of the instruments for further treatment.'

EH: Documentation of processes is necessary from a regulatory perspective, as well as for quality management guidelines. Does the Trison 4000 offer this?

Knuth: 'Documentation of all individual steps may be considered time-consuming, but it provides user safety. Comprehensive process documentation guards against potential situations where users may have to provide explanations, meaning that, if something was not documented, it was not done.

'All users should safeguard against this, which is why the Trison 4000 generates a protocol of the last cycle after each treatment. This protocol documents all relevant parameters and can be securely, digitally archived via a USB interface or through integration into the network.'



TRISON 4000: Ultrasonic bath for the intensive and gentle pre-cleaning of robotic instruments

With all these advantages, there must surely also be a disadvantage – I assume the system is not particularly cheap?

'A complex device like this has its price. But the big advantage is that there is hardly any staff expenditure. The instruments are inserted, the device is started, and the instruments can be removed for further treatment after only 30 minutes. Over a long period of time, this represents a substantial time saving and clear benefits for staff in the CSSD.'

And the device makes manual labour unnecessary?

'We have various examinations and test reports which show that pre-cleaning in the Trison 4000 is successfully carried out almost without needing any additional manual steps. The device was launched in 2017. More than 60 systems are currently in use in validated procedures across Europe, and user feedback is always positive. They especially value the intuitive handling, excellent cleaning results and the considerable relief in stressful working conditions.'

Could you give us a view into the future?

'Robot-assisted surgery will continue to increase. There will be more providers of robotic systems, along with completely new technologies, new instruments and new procedures which will continue to alleviate and improve the treatment of patients. The Trison will be ready for the cleaning of new robotic instruments in future.

Bandelin always has an eye on new developments to ensure we can continue to meet this demand with innovative ultrasound equipment and to contribute to resource-saving cleaning of medical instruments.'

Florian Knuth studied economics in Berlin and is currently Sales Director of the Medical Division of Bandelin. He is responsible for consulting and sales of all medical ultrasonic baths used in CSSDs and medical practices.
With almost ten years professional experience in the medical field, he is an expert in instrument reprocessing and decontamination applications.
His knowledge and the constant exchange with the users help him understand the users' needs and requirements in their daily work.

puts cleansing methods to the test

rilisation is gold standard

less steel carriers with a failure rate of 0% for steam, and 1.9% and 1.9% for EO and HPGP, but the failure rate for VHP was 76.3%.

'The results illustrate that steam sterilisation is the most effective and robust sterilisation technology and has the largest margin of safety and is the least affected by protein, salt and lubricants,' said Dr Rutala. 'VHP has a significantly narrower margin of safety in killing vegetative bacteria and spores in the presence of a salt and serum challenge.'

The findings have implications within healthcare settings.

Contamination of surgical instruments does occur, but is observed and rarely reaches the patient

Dr Rutala said: 'Surgical instruments that enter sterile tissue should be sterile because microbial contamination could result in disease transmission.

Despite careful surgical instrument reprocessing, surgeons and other healthcare personnel describe cases in which surgical instruments have been contaminated with organic material (e.g. blood). While most of these cases are observed before the instrument reaches the patient, in some cases the contaminated instrument does indeed contaminate the sterile field or, rarely, the patient.' Researchers say data from this study will help clinicians in infection prevention to assess the patients infection risk when a contaminated instrument is unintentionally brought into the operating room, or used on a patient.

'The study reinforces the need for meticulous cleaning and reliable and validated cleaning monitoring methods that are predictive of an infection risk,' Rutala concluded.

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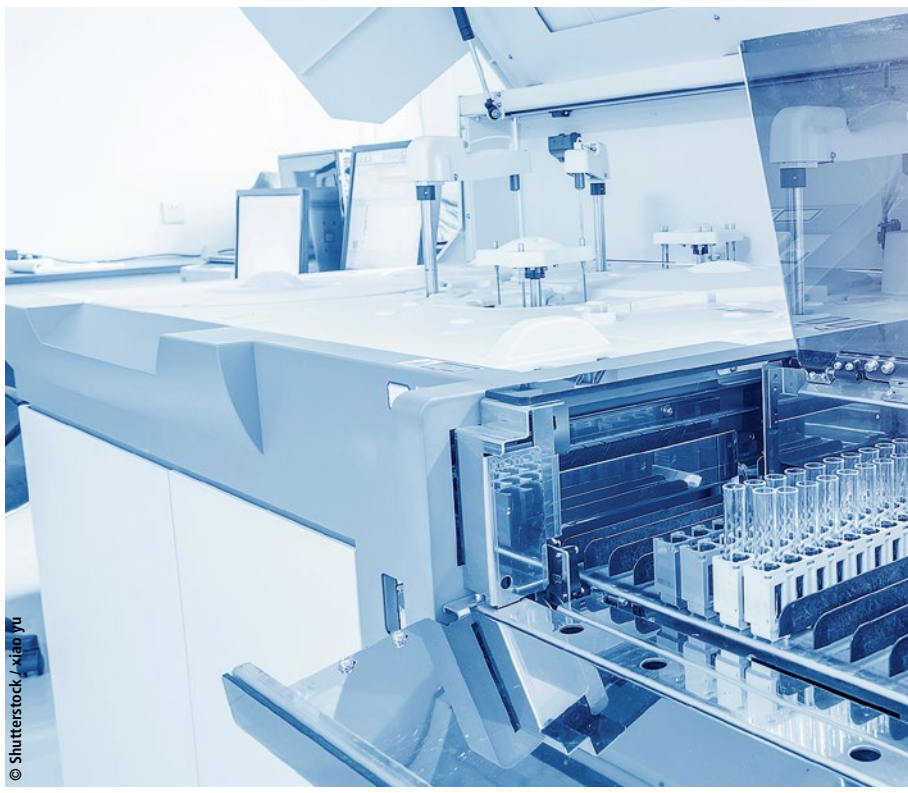
Increased lab quality – because of, or despi

Economic aspects and COVI

The academic teaching Karlsruhe Hospital, at the University of Freiburg, is the largest hospital providing tertiary care in the Middle Upper Rhine Valley. Every year, 63,000 in-patients and 180,000 out-patients are treated in the 1,500-bed facility with 50 departments and 30 out-patient clinics. Inevitably, a hospital of this size has a central lab. *EH correspondent Walter Depner* spoke with *Dr Horst Mayer, managing senior physician of the Department of Clinical Diagnostics*, about the lab and particularly automation, introduced there over recent years. The effects on the lab of COVID-19 were also explored.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Currently, the hospital has 38 full-time employees and 12 full-time support staff – mainly students. The trauma and emergency department admits about 35,000 adult patients per annum. 'Each day, we process on average 4,000 samples, of which approximately 1,500 are serum, 500 are coagulation and 800 are blood tests,' explained Mayer, speaking of the lab's involvement. 'The remainder is made up of all other materials. In toto, this amounts to 16,000 analyses per day. Peak times are between 7-9 am. In that window, we receive 800 samples; the rest is spread more or less evenly over the day.'

EH: A hospital lab usually processes more pathology samples than non-hospital labs. Is this the case in Karlsruhe?

Mayer: 'Indeed. Here about 30 percent of the individual samples are pathology samples; in a non-hospital lab group this would be about five percent.'

Over recent years, hospital length of stay has been shrinking, while patient throughput has increased significantly, thus also increasing the number of samples arriving in the lab and thus encouraging lab automation. Does that mean there is less time for analytics?

'Definitely. We started automation more than ten years ago with a Siemens Flexlab. This automated lab system generated major benefits, because it could be operated even with a very small team. It ran 24/7 and made a marked improvement because length of stay decreased and throughput increased. The new lab system, which has been installed since, offers even shorter turn-around times as well as significant quality improvements. In fact, at this point we are not running to capacity.'

Not all areas present themselves for the same degree of automation; take mass spectrometry, special microtiter serology or pathology. What is the situation in Karlsruhe? Where did you start automation and where could the most significant effects be realised?

'Obviously, there are limits to what is feasible. In terms of technology we could link a Sciex 5600 mass spectrometer to the lab system. However, I don't consider this particularly useful at this point. Assays, which are currently performed as ELISA on MT, that is microtiter plate basis, but which can be done in an immunoassay analyser linked to the system, are all transferred.'

If you rank clinical disciplines by degree of automation, where would you place clinical chemistry?

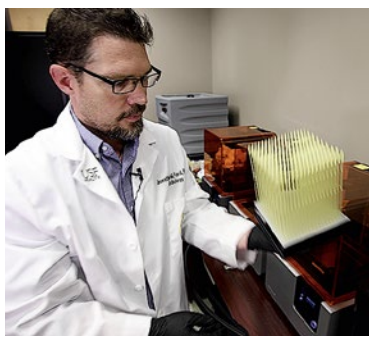
'Indeed we do old-school clinical chemistry, around the clock – tumour markers, hormones and infection serology. Currently, I still consider conventional clinical chemistry relevant. Going forward, however, I think this will change over the next 10 to 15 years. Current resource-intensive methods will be replaced by molecular biology analyses, in particular their miniaturisation will be influential. In a nutshell: traditional clinical chemistry in its current form will have become obsolete.'

How did your staff structure change over recent years due to automation? Did you have to or were you able to switch staff? Did you ease the burden in labour-

Rapidly meeting a surging demand

The science behind 3-D prin nasal swabs

Medical device approved 3-D printers are producing clinically safe and effective nasopharyngeal swabs for COVID-19 testing.


Jonathan Ford PhD, is a biomedical engineer and fellow medical printing expert model


Summer Decker, PhD, is a 3-D Clinical Applications director and imaging scientist

Report: Cynthia E. Keen

A nasal swab may seem rudimentary, but is essential for testing COVID-19 diagnostic test kits and components – nasal swabs, collection vials, and chemical reagents – have been in short supply worldwide, especially in March. Ironically, nasopharyngeal swabs are predominantly manufactured in northern Italy and China, two countries first impacted by coronavirus.

Concerned by diminishing supplies and near impossibility to restock, the dean of the University South Florida (USF) Morsani College of Medicine, wondered if the radiology department's 3-D Clinical Application Division could produce swabs.

3-D Clinical Applications director and imaging scientist Summer Decker PhD, with Jonathan Ford PhD, biomedical engineer and fellow medical printing expert model, create virtual analyses for simulations of injury mechanics and blood flow, for example, as well as 3-D prints of anatomical models of organs and regions of the body.

In two decades of research they produced trailblazing work and numerous publications. Worldwide, their lab, located at USF Health and Tampa General Hospital, is one in about two dozen renowned for this expertise.

Immediately investigating the idea, they started to develop nasopharyngeal swab prototypes that would use materials cleared by the USA's FDA as patient-safe. They received one representative standard-of-care nasopharyngeal swab to examine before creating a new design for a 3-D printer.

'On the surface, creating a nasopharyngeal swab doesn't seem that complicated a design,' Decker observed. 'But it's more complicated than it looks. We knew we couldn't replicate components of the traditional swab, such as the flocking on the tip which collects the sample. We needed a device that could be printed as one unit, collect a sufficient mucosal and epithelial sample for viral testing, and be safe and comfortable during the collection process. Additionally, the material could not interfere with the actual testing machines.'

Decker and Ford sought ideas and advice from colleagues. They also invited 3-D medical printing expert Todd Goldstein PhD, director of Northwell Health and 3-D Design and Innovation Center, in Manhasset, NY. The final design team included the 3-D medical printing experts, infectious disease physicians, otolaryngologists, a virologist, and a pulmonary radiologist who suggested rounded 'nubs' on the tip of the swab to maximise surface area to collect a sample.

Ultimately, 12 designs were investigated and prototypes printed. The prototypes were given to the design team physicians for feedback and consensus. Hospital residents and the design team tested the prototypes on themselves to identify the most comfortable designs.

The final design was a standard-length swab with a tip that has a smooth cap on the top to protect the tissue as it goes through the nasal passage. Nubs or ridges in a staggered pattern around the sides collect the sample as it goes into the nose.

An expert virologist performed robust bench lab testing to verify that the swab design would grab enough sample and met viral load detection requirements. The length of time the swab could hold a sample was measured. The swab also underwent rigorous compatibility testing for the collection media and the virus testing machines.

The team contacted Formlabs, a digital fabrication company and licensed medical device manufacturer based in Somerville, MA, which manufactures professional 3-D printers. The company worked with USF to optimise the design and production of the prototype swabs.

'Swab sticks have an intentionally weak point 7-8 cm from the tip, which allows the stick to be broken to the correct length so that the vial can be capped before transportation to a laboratory for testing,' explained Stephan Hollaender, Formlabs' managing director EMEA. 'The most difficult part of designing these swabs to be 3-D printed was ensuring the material was strong enough to be used in a patient's nose without fear of it breaking, and weak enough that it can be easily snapped and put in a vail.'

USF and Northwell rapidly conducted a 120-person trial comparing the performance of the 3-D-printed swab with a traditional one. The 3-D printed swab performed as hoped, but to make sure, the clinical trial expanded to include 35 hospitals nationwide.

Goldstein's team is conducting the 3-D printing work for all of Northwell Health, which is a 23-hospital healthcare provider in New York state, the epicentre of the crisis in the USA. 'We have eight Formlabs' 3-D printers with the capacity to print about 4,000 swabs a day. By the end of May, the lab had printed over 90,000 swabs which were distributed among Northwell Health hospitals and outpatient facilities,' Goldstein said.

'In our efforts to bring nasopharyngeal swabs into production in record time, we helped supply the Northwell Health system with a critical diagnostic tool needed to combat this disease. In a time of crisis, it is ingenuity and innovation that helped keep everyone motivated to help our community as best we can.'

Formlabs is manufacturing the nasophangeal swabs in its 200 3-D printer manufacturing facility in Ohio, and has the capacity to produce up to 100,000 swabs a day when printing capabilities are fully ramped up. 'We are pricing the swabs to cover their production cost and the investment we made to ramp up production,' Hollaender explained. 'We do not intend to produce these swabs long term.'

The USF 3-D Imaging Lab holds a provision patent for the swab with Northwell Health. USF made a decision to share the files with any hospital that has a Formlabs printer through April 2021, Decker explained.

te automation?

ID-19

intensive areas and transfer people to more 'demanding' tasks?
'When we installed the first automated lab system in 2009, we were lucky because the four employees who became redundant retired – we did not have to replace them. Over the course of time we reduced the team in the core lab and transferred some team members to special diagnostics, haematology, coagulation or areas such as serology or toxicology.'

A hospital lab always reflects the foci and departments of an institution as a whole. In your case, paediatric and adult oncology are major departments. How does this affect your lab?
'We see a significant demand by the oncology departments and this plays a major role in the lab. We were able to transfer several of the clinical chemistry staff mentioned above to oncology. In haematology, we have a Sysmex system with digital morphology followed by flow cytometry. Among the areas that are not part of the central lab are molecular biology, where PCRs for oncology and pathology are performed.'

Talking about PCR: how does COVID-19 affect your lab?
'Not so much. We do have a full Cobas 6800 system. The main issue, however, is the fact that we don't have enough tests. Currently, we use Corona antibody tests.'

Do you only test your own patients and staff or do you also receive samples from outside to process?
'We receive very few external samples from office-based physicians. Our problem is the fact that non-hospital labs receive priority for tests. We only receive about 1,000 test units per week for molecular biology. Technically, we would have the capacities for many more tests. I personally was not tested, since the lab is considered a closed-off zone. The situation is obviously very different for our patients and the care staff.'

Formerly a laboratory physician in Magdeburg, Germany, 20 years ago Dr **Horst Mayer** joined the Department of Clinical Diagnostics at Karlsruhe Hospital, where he became managing senior physician.

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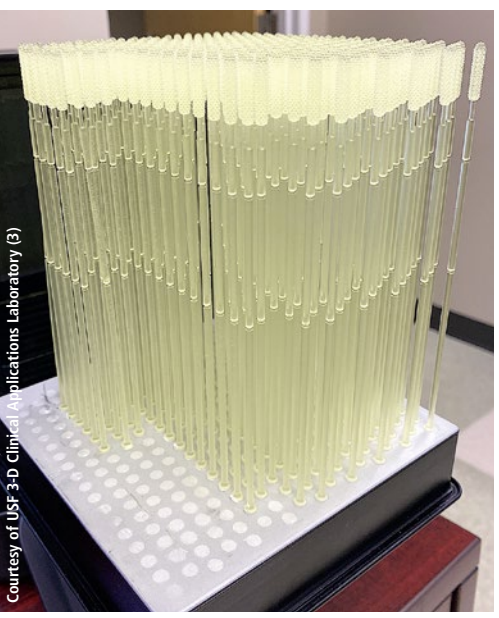


Courtesy of USF 3-D Clinical Applications Laboratory (3)

3-D printed swabs

Her lab is printing 324 swabs a time per printer using Formlabs surgical guide resin, a process taking between 15 to 30 hours depending on printer model used. After the swabs are printed, they are cured, individually wrapped, and autoclaved, and ultimately delivered to USF and Tampa General Hospital's infectious disease labs for coronavirus testing.

More than 3,000 Formlabs 3-D printer customers worldwide have signed up to print COVID-19 response parts. 'Formlabs and its partners have produced more than a million swabs so far, and thousands of other medical components and PPE supplies,' said Hollaender.

* Healthcare groups wanting to legally produce swabs may contact Dr Decker: 3dclinicalapplications@usf.edu.

Abbott: Creating Life Changing Technology

An increasingly dynamic cardiovascular presence

In the world of laboratory diagnostics, 'Abbott' is a household name. Few people however are aware of the fact that the company, headquartered in Illinois, USA, is also leading in other fields. A number of innovations in cardiac and vascular diagnostics and therapy might soon put Abbott in the limelight. Dr Angela Germer, Regional Director DACH, and Volker Keller, Head of Marketing DACH, Vascular at Abbott, updated Daniela Zimmermann on the company's most recent developments and the plans for the future.

Abbott's German cardiovascular business area operates from Wetzlar and Eschborn, in the Frankfurt/Main region, with Vascular und Structural Heart managed in Wetzlar. Whilst the Structural Heart team focuses on the treatment of structural heart disease (SDH), the Vascular team's expertise lies in diagnosis and treatment of vascular conditions with systems to assess vascular physiology, guide wires, and drug-eluting, as well as non-drug eluting, balloons and stents.

From left: Volker Keller, Head of Marketing for DACH, Vascular at Abbott, Dr Angela Germer, Regional Director DACH and Astrid Tinnemans, who heads Public Affairs in Germany, updated Daniela Zimmermann on the company's most recent developments and its plans for the future.

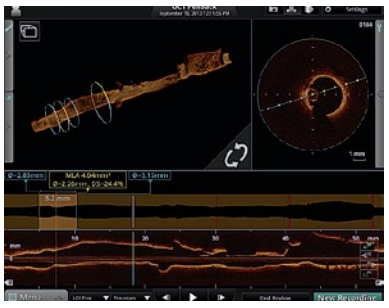
OCT and FFR to avoid unnecessary stents

Today, some patients receive stents without proven ischaemia, on suspicion so to speak. Usually, two techniques are used to assess ischaemia: either fractional flow reserve (FFR) or resting full-cycle ratio (RFR). A specially designed pressure wire looks for drops in pressure caused by a stenosis. If the pressure drops significantly, the oxygen supply to the heart is impeded, says Dr. Angela Germer.

Abbott uses a two-pronged approach to ensure that stents are implanted when and where clinically needed and to improve patient outcomes: firstly, the guidewire PressureWire™ X uses wireless data transmission, thus facilitating ischaemia assessment by FFR; secondly, the Abbott-developed imaging solution OCT (optical coherence tomography) which allows precise measurement of vessels. 'With this approach, we aim to optimise percutaneous coronary interventions, PCI for short, and to increase the likelihood that the right stent is placed at the right location,' Dr Angela Germer explains. OCT delivers high-resolution colour images to monitor vessels prior to the intervention as well as in the follow-up when the stent is checked for correct placement and functionality.

Abbott supports physician training with modern technologies, such as virtual reality (VR). In cooperation with several hospitals, the company recorded catheter-based procedures, such as FFR und OCT, and turned them into 3-D simulations to be used with VR headsets. 'Thus, interventions can be practised virtually, which increases patient safety during the actual procedure,' Volker Keller points out. Abbott and the international cardiologist working group (AGIK) jointly organise workshops at trade fairs and congresses, and in hospitals, to provide in-depth training for clinical staff.

The pressure wire is also used to diagnose microvascular heart disease which, in Germany alone, affects 175,000 people, Dr. Germer says: 'This condition is rather frequent among cardiac patients, but difficult to diagnose. Many patients present several times without the cardiologist being able to detect the root cause. Our PressureWire X, combined with a dedicated software solution, can help detect minute deposits in the vessels and thus identify the disease.'



OCT delivers high-resolution images of vessels

The highly specialised Abbott stent portfolio covers the many requirements the tiny support structures have to fulfil in the different anatomies. Stents for the femoral artery, for example, must be able to withstand enormous biomechanical forces, such as torsion. 'The nitinol wires in our Supera stent are not lasered but woven,' Germer explains. 'This unique technology makes Supera much sturdier than conventional stents, whilst maintaining its flexibility.'

Closure system accelerates patient mobility

Perclose ProGlide, the tried and tested closure system that deploys suture after endovascular procedures with a femoral puncture larger than 5F without the use of collagen, is now also indicated for the femoral vein. 'A suture is placed right at the vessel wall and the edges are joined again initiating primary healing. The closure can be tested right after the intervention. Unlike conventional sutures, Perclose ProGlide allows the patient to get up and move around quickly,' explains Dr. Germer. Thus, hospital length of stay is reduced and accompanying procedures, such as a bladder catheter, can be avoided. Another advantage: If re-access is necessary, which is, in fact, the case with several conditions, the very same site can be used, even right after the initial procedure.

Today, patients benefit hugely from implantable cardiac support systems, such as LVAD (left ventricular assist device). Abbott is currently developing the next-generation of such a device: FILVAS, fully implantable left ventricular assist system. It has no external components, such as battery packs or charging ports, which patients have to carry 24/7. FILVAS was recently designated a Breakthrough Device by the USA's FDA. 'Obviously, the new implant has to be charged regularly as well,' Keller explains, 'but FILVAS does this by induction via an implanted coil.' Since energy supply does not require opening the abdomen, patients can bathe, swim, enjoy the sauna – these are activities that are almost, or even entirely, impossible with LVAD. Not to mention the fact that in conventional systems the external energy supply opening is a potential door for infections to enter the body.

AI algorithm calculates infarction risk

Abbott not only uses diagnostic and treatment devices to improve cardiac patient care but also designs solutions based on artificial intelligence (AI). A recently developed AI-based algorithm to assess infarction risk is about to be used in clinical settings. The Abbott R&D team benefited from the in-house lab medical expertise: 'Our algorithm correlates troponin values with other patient data, such as age, gender or prior disease,' Keller points out. 'This allows a detailed assessment of individual infarction risk.' Prior to the commercial launch of the algorithm, clinical tests need to be concluded but, so far, the studies have yielded very promising results [Circulation: https://doi.org/10.1161/CIRCULATIONAHA.119.041980].

With these ambitious projects in the wings, Abbott is well positioned to expand its reputation beyond the lab and have a strong impact in cardiovascular medicine.

When classic ventilation therapy fails in COVID-19 cases

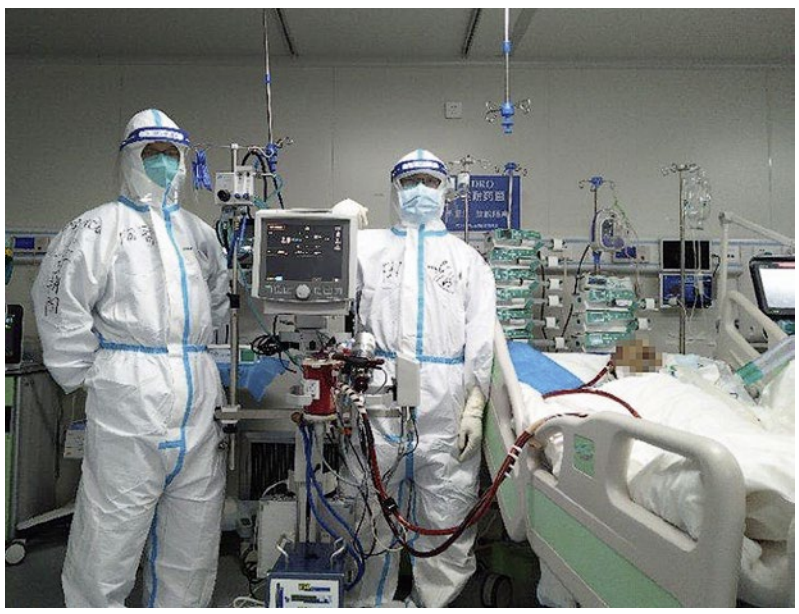
Extracorporeal therapy use rises

'As the coronavirus spreads and infections with COVID-19 further increase throughout Europe, **E**xtra**c**orporeal **M**embrane **O**xygenation (ECMO) therapy turns out to be a necessary option for patients with severe courses,' Xenios AG reports. The company's ECMO consoles can provide support in cases of severe pneumonia and ARDS with lung failure. 'However,' the company points out, 'in contrast to the ventilation methods usually used in these cases, the extracorporeal method is usually only used if the classic ventilation therapy is not effective or not effective enough.

'For critically ill COVID-19 patients with acute lung failure and refractory hypoxemia, despite use of all standard therapy related measures, our treatment often remains the last therapeutic option and, in the best case, is a lifesaver for these patients,' adds Dr Jürgen Böhm, Chief Medical Officer of Xenios.

Bypassing lung function, the system clears the patient's blood of carbon dioxide outside the body and enriches it with oxygen, giving lungs time to heal. 'Because of the increase of critically ill COVID-19 patients, more physicians will opt for ECMO therapy.' The company reports significantly higher demand for the devices and patient kits and has increased production of ECMO consoles. The devices are already in use in many COVID-19 hot spots such as in Italy, Spain and France, and beyond Europe. China's most affected region Wuhan received a delivery of ECMO consoles and patient kits in February.

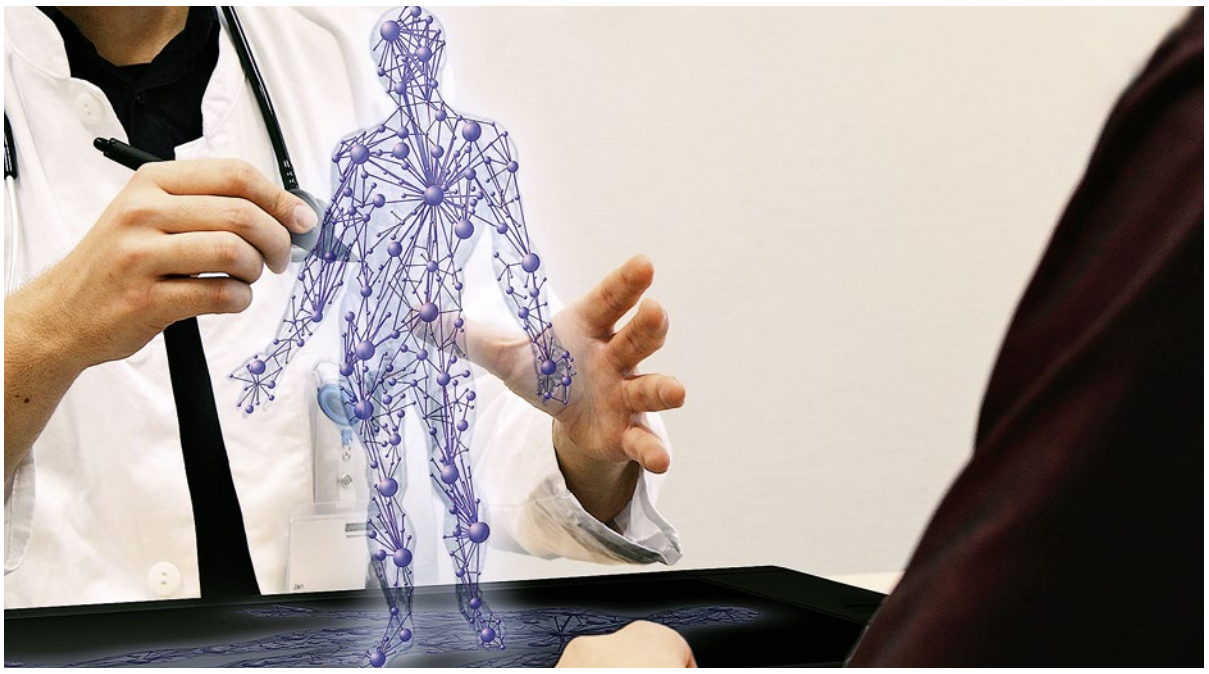
'Our biggest challenge now is availability of specific components for our products,' said Dr Andreas Terpin, Chief Executive Manager of Xenios, who also underlined the need to meet various standards, for example, the CE mark and FDA clearance (approved by the USA's FDA through Fresenius Medical Care North America earlier in 2020). The system is available in more than 50 markets worldwide.



Training intensity has been ramped up to ensure safety and straightforward use of the devices and is provided internationally via video transmission.

Advancing personalised medicine in clinical routine

The virtual medical assistant and digital patient twin



Report: Katrin Schreiter

Siri and Alexa are leading the way: virtual assistants meet many daily needs. Soon, similarly programed software and a 'digital patient twin', will be launched into the medical world – both IT applications based on Artificial Intelligence (AI).

The virtual medical assistant and digital patient twin are two key aspects of a research project 'Models for Personalised Medicine'. Scientists at the Innovation Centre for Computer Assisted Surgery (ICCAS) in the Medical Faculty at Leipzig University aim to use these tools to improve the treatment of cancer patients.

The project has received funding of around €5.1 million from the Federal Ministry of Education and Research and is being implemented with the help of companies in the Free State of Saxony, in eastern Germany.

Different technologies have been designed with various pilot applications: 'The objective is to support the medical treatment of cancer patients with the help of IT,' explains Professor Thomas Neumuth, who heads the project at ICCAS, and is also the Deputy Director of the centre. Targets include, for instance, patients with head/neck tumours.

IT support starts with the tumour board, i.e. interdisciplinary discussion between surgeons, radiologists, radiotherapists or pathologists. 'Experts from different medical disciplines discuss the medical condition of the respective patient,' Neumuth explains.

'It's a type of briefing where all information relevant to the decision-making process is evaluated. The experts discuss treatment options based on this information and make a joint decision,' he explains.

In the future, the virtual assistant is to be present at these discussions as well. 'This means we won't lose any information,' he points out. However, among programming challenges will be the different volumes of sound and different positions of those who are talking in the room, which must be detected and accounted for.

'Unclear pronunciation or strong accents should also not impact on word recognition.' In contrast to conventional software, language recognition used in the context of medicine must be programmed for the specialist terminology and must also adhere to the strictest guidelines on confidentiality.

The Leipzig-based scientists have another vision: the so-called digital twin. This is an organised collection of all information about a patient and their anamnesis: radiological images, information on underlying medical conditions and previous surgery as well as molecular-genetic data. 'This is much more complex than the electronic patient file which we already have,' Neumuth observes.

The data in the patient file has not yet been linked in a meaningful way, so comprehensive, patient-specific analyses supported by AI is not yet possible. However, the digital twin now 'paves the way for the step from the analogue into the digital world,' he believes.

This also includes storing treatment steps, playing through options, and updating information, explains the project manager. This objectivises medical work, makes information accessible to all experts in the team in equal measure and facilitates improved prediction of the effectiveness of treatment.

During diagnosis and therapy, the information of the data twin is compared to digital models of the clinical picture, which are optimised with the relevant studies and latest scientific findings. The computer should then support doctors with personalised treatment recommendations for cancer patients. 'The final decision on treatment will obviously continue to be made jointly by patients and doctors,' Neumuth points out.

It is also envisaged that a patient-data explorer will link patient data from radiological images and medical reports via web technology, and that it will integrate molecular-genetic tumour information into the decision-making process, or calculate patient-specific therapy profiles for surgery and radio or chemotherapy. 'Different types of information contained in the digital twin should be directly linked and analysed by AI,' Neumuth adds.

Many developments and tests are still needed to ensure that this and other technologies in the field of personalised cancer medicine can be directly integrated into clinical routine. 'This will take three to five years,' he estimates.

'The objective is to create a scientific and methodological basis for personalised cancer treatment assisted by AI. In the ideal case, this means that a patient will receive personalised treatment based on the latest scientific findings, which takes into account the patient's personal situation and specific needs, with everything being transparent and explained in an understandable way.

Professor Thomas Neumuth is an engineer and IT specialist. His research focuses on model-based medicine, intelligent biomedical technology, and medical IT systems. Born in Leipzig, he is the technical director of the Innovation Centre Computer Assisted Surgery (ICCAS) and heads the ICCAS Research Department for Model-based Medicine. His work on intelligent medical IT systems was chosen as a reference project for the Digital Summit 2017 by the Federal Ministry of Education and Research and confirms the position of the ICCAS as one of the leading research centres in Germany.

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SPECIAL REPORT: The long-term impact of COVID-19

On the rise: Internal and external radiology

The coronavirus pandemic – an international tragedy – created unprecedented upheaval and challenges within health systems, economies, and society. In hospitals, new ways of working had to evolve. Social distancing led to virtual consultations and teleradiology has found an added dimension, with its success, practicality, and effectiveness likely to see more widespread future use. *Mark Nicholls* asked three radiologists about the relevance of teleradiology during the epidemic, and what the future holds.

Evidence collected during the SARS-CoV-2 pandemic by a team from the University of Tennessee, USA, clearly showed changing patterns in the use of teleradiology. Dr Mohammed Quraishi, Assistant Professor of Radiology, Section Chief of Body Imaging and Informatics Director at the University of Tennessee Medical Center, believes the term "teleradiology" needs disambiguation. 'Often it brings to mind a radiologist far removed geographically, perhaps in a different country, reading for multiple hospitals with limited rapport with any specific hospital,' he said. 'I would term this "external teleradiology", because the radiologist is external to the local group. It's important to differentiate this from "internal teleradiology" where a radiologist, employed by the practice, reads remotely.'

In the USA, practices during the pandemic increased internal teleradiology, and significantly decreased external teleradiology. 'The reason seems two-fold,' Quraishi surmised. 'First, removing radiologists from the hospital makes sense when trying to mitigate the risk of contracting SARS-CoV-2 and, second, the increase in internal teleradiology – as opposed to external teleradiology – was almost certainly due to the drastic decrease in case volume.'

Whilst, traditionally, internal and external teleradiology have been used for on-call and overnight shifts for emergency radiology cases, daytime shifts during the pandemic were transferred to internal teleradiology – bringing off-site reading into the daily fold to help decrease radiologist exposure to potential SARS-CoV-2 infection, and allowing radiologists to work at home.

The increased use of internal teleradiology was seen throughout the USA – particularly in the northeast, where the pandemic had prevalence.

To gauge changing teleradiology use, the group queried 290 locations, representing a geographically diverse cross section of institutions. They found an overall jump in the proportion of sites installing home workstations (65.2%) and switching normal daytime shifts to internal teleradiology (73.6%). Around 56% of respondents said they saw enough benefit from the experience that they plan to continue similar workflows post-COVID.

Specifically, 64.8% reported decreased stress levels, and 96% found improved or no change in turnaround times, a position Quraishi echoed from his personal experience. 'I found internal teleradiology less stressful, with an overall increase in productivity,' he said. 'Radiologists also reported less interruptions at home allowing them to focus on interpreting studies.'

He believes the pandemic will see a change of emphasis in the use of teleradiology, with practices re-evaluating teleradiology with new business models, services and workflows, such as second opinion reads or even practices sending out studies for subspecialty interpretations.

Teleradiology to fight burnout problems

Given increased evidence of radiologist burnout and demands for better work/life balance, teleradiology might offer a solution. 'According to our survey, the majority of groups plan to incorporate internal teleradiology into the post-pandemic workflow. I predict internal teleradiology will rise across the country and, as groups get comfortable with that, there will likely be spill over into external teleradiology.'

Former NHS consultant Dr Stephen Davies, now Medical Director of the Medica Group, a business providing teleradiology services to the NHS, said: 'Working from home using teleradiology has allowed radiology teams to work "in hospital" and out of hospital on rotation and increase opportunity for social distancing.'

Medica has facilitated "pass through" home reporting for radiologists to undertake their NHS sessional work using Medica's existing image transmission and reporting.

'The culture shift towards using technology to enable high-quality home working has risen during the COVID-19 crisis,' he pointed out.

Teleradiology has been used across the scope of diagnostic imaging, from emergency reporting – stroke and COVID chest X-rays – to elective imaging, and geographically this has been 'without boundaries and is widespread'.

Foreseeing a long-term growth

'Teleradiology has been on a long-term growth trajectory and this will continue,' Davies predicted. 'COVID has increased the understanding of working from home. Teleradiology providers deliver a scalable, flexible quality assured reporting service which can respond to geography, reporting demand, time constraints and subspecialty constraints.'

He believes post-crisis teleradiology will become a bigger part of daily work routine with radiology services finding a new balance between "in house" face-to-face radiology and protected and uninterrupted teleradiology home working. However, Davies has noted a downturn in volumes for all teleradiology services during the crisis, primarily due to a fall in elective work and emergency cases during lockdown, although, as restrictions ease, elective imaging services are increasing.

Yet over the last decade, Dr Davies said teleradiology has been growing and is part of service provision for more than 90% of the NHS, with the delivery technology becoming ever-more sophisticated. That now sees the Medica Group offering a round-the-clock service across 90 UK hospitals.

'The more experienced users of teleradiology have integrated the provision into their service in a seamless fashion. I expect this trend to continue and increase,' he added.

Key lessons have been learned in teleradiology use during the epidemic, primarily from the NHS, rather than teleradiology companies – particularly 'successful teleradiology replicating NHS office radiology requires more than simple deployment of a workstation over simple domestic broadband.

'Teleradiology,' he predicts, 'will continue to become more sophisticated with increasingly advanced operational delivery and image review, both supported by artificial intelligence. Its penetration will increase into the provision of radiology reporting both emergency and elective work and will also use its platform and operational expertise to deliver emerging digital telepathology.'

With the Basel area a COVID-19 hotspot in Switzerland, the Department of Radiology at the University Hospital Basel provided support via its teleradiology capability.

As cases rose in March, the unit – which delivers regular teleradiology services to local and regional hospitals at night and weekends – introduced a structured CT reporting template for COVID-19 cases that included quantification of lung opacifications. 'Around the peak of new infections in Switzerland at the end of March,' said Dr Thomas Weikert, resident at the department, 'we saw increasing numbers of CTs performed with the question of COVID-19 associated pulmonary infiltrates rising by +17% a day.

'If that continued, we would have been in serious trouble very quickly. Luckily, the curve flattened during April as rigid public health measures taken by the Swiss authorities brought the number of new infections down. We were also developing automated quantification pipelines to prepare for the situation where it was not possible to conduct all the analyses manually.'

For COVID cases, lung segmentation was conducted and via density thresholding, the percentage of lung tissue affected by infiltrates was established. 'This is very useful for clinicians especially when it comes to follow-up. It is about quantifying COVID-related changes.'

The unit (which also runs an international expert teleradiology reading program to provide structured reporting on Idiopathic Pulmonary Fibrosis (IPF) cases, which allows hospitals in Central Eastern Europe and Asia to send high-resolution chest CTs of suspected IPF to the university hospital), has continued to provide structured COVID-19 reports to local/regional partner hospitals via teleradiology.

The value of teleradiology during the pandemic has been apparent and the Basel department monitored its growth during this period with an internal RIS/PACS crawling tool, allowing them to identify all exams with COVID-19 related clinical questions.

'Teleradiology for COVID-19 cases can prove beneficial in three respects. First,' Weikert continued, 'by promoting structured reporting, including quantification of pulmonary changes; second, should regional hotspots arise in the future, overwhelming capacities of the regional health service providers, teleradiology could share the diagnostic workload with radiology departments in less affected areas; third, by automatically analysing cases from many regions, it could be part of a regional outbreak early warning system. If many exams are diagnosed with COVID-19-suspected pulmonary changes, a warning signal could be sent to the authorities.

'I think, in a broader way, telemedicine, which includes teleradiology and provision of services of other specialties, will get a profound boost by this, because there are many people who used telemedicine for the first time and I think they will continue to use that.'

Consequently, Weikert expects the role of telemedicine and teleradiology to rise independently of the current public health crisis.

Dr Mohammed I Quraishi is Assistant Professor of Radiology, Section Chief of Body Imaging and Informatics Director at the University of Tennessee. He researches data analytics and medicine, working towards ultimately improving patient care through advancing healthcare efficiency, diagnostic accuracy, cost-savings, and mitigation of physician burn-out.

Dr Stephen Davies is Medical Director of the Medica Group and Fulltime Executive Director. A former NHS radiologist, with more than 25 years' experience as a consultant radiologist within the NHS, he is also a Past President of the British Institute of Radiology.

Dr Thomas Weikert is a resident in the Department of Radiology at University Hospital Basel, Switzerland, where he researches translation of digital solutions in medicine and is involved in an evaluation of the IPF teleradiology program.

Physiopathological hypothesis needs validation on post-mortem studies

We need a global view of COVID-19

Anand Devaraj is Professor of Practice in Thoracic Imaging at Imperial College London's National Heart and Lung Institute and a consultant thoracic radiologist at the Royal Brompton Hospital in London, UK.

Mickaël Ohana is a professor of radiology at the University of Strasbourg and radiologist at Strasbourg University Hospital in France. He specialises in non-invasive cardiovascular and chest imaging.

Myriam Edjlali-Goujon is a neuroradiologist at Hôpital Raymond-Poincaré, Paris-Saclay University, France.

There are major complications from COVID-19 – ARDS, pulmonary embolism and neurological – that imaging can help detect, manage and/or follow up in the long term, radiologists from France and the UK explained during a recent ESR Connect session.

Report: Mélisande Rouger

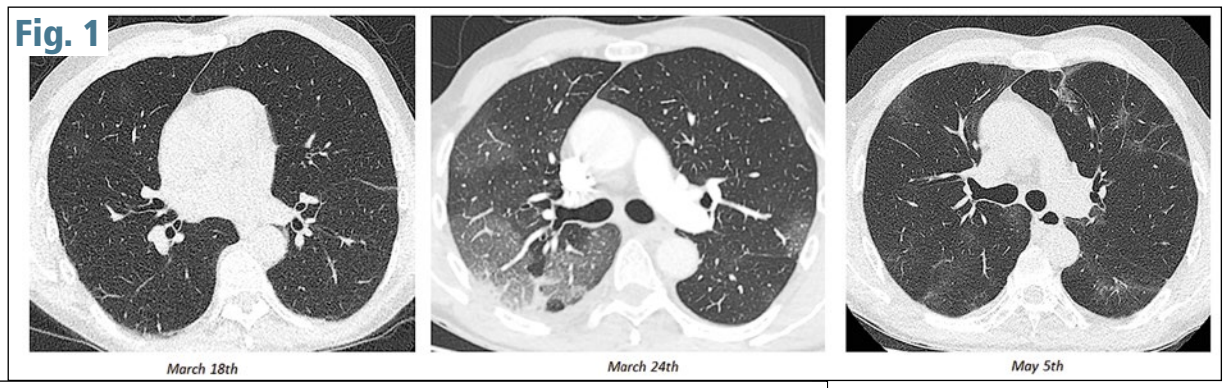


Fig 1: Good evolution of a COVID-19, with almost normal initial chest CT at D3, extensive ground glass opacities (GGO) at D9 and almost complete resolution with limited residual GGO at six weeks

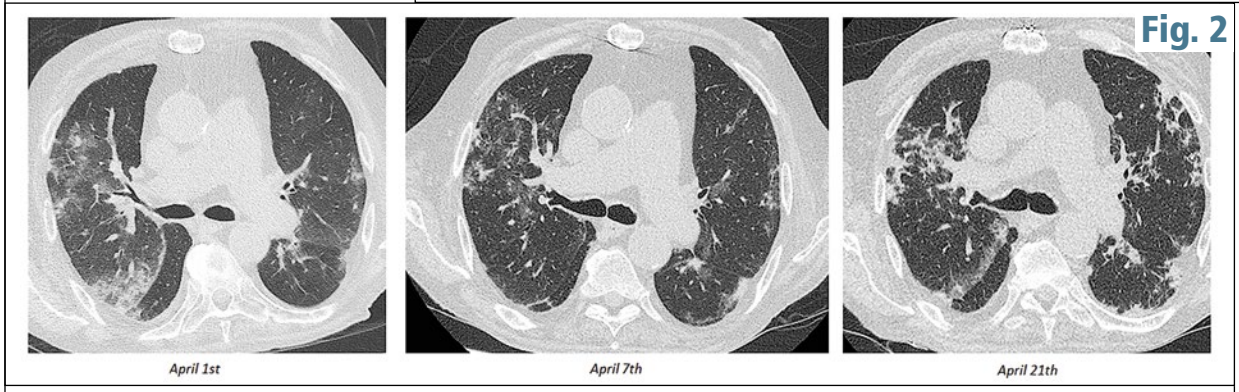


Fig 2: Moderate GGO and alveolar consolidations on initial Chest CT at D7, evolving towards reticulations at D14 and with pattern of organising pneumonia and traction bronchiolectasis at three weeks. Whether these lesions will completely resolve or not at further follow-up is still unknown

ARDS – Acute respiratory distress syndrome (ARDS) is the most dreaded complication and the number one morbidity in COVID-19 patients. The incidence was up to 30% of patients in initial reports. In Strasbourg University Hospital, at epidemic peak, there was an 8% rate of admission to ICU directly after ED admission because of ARDS, according to Mickaël Ohana, a local professor of radiology who specialises in non-invasive cardiovascular and chest imaging.

ARDS diagnosis is not based solely on imaging, but, in line with Berlin criteria, is based on acute hypoxemia plus bilateral radiographic opacities, through chest X-ray or chest CT. 'The problem is not diagnosis – it is prediction and follow-up,' Ohana said.

Prediction – Few papers have tried to score the risk of ARDS from an initial chest CT of a COVID-19 patient, based on either quantitative or visual assessment. But these types of semi-quantitative scores are not highly reproducible, not standardised, and are time-consuming.

'I would advise simply using the ESR/ESTI visual scale, which is based on the extension of the lesions over the lung parenchyma, and then classifying in five different levels. This is a very simple visual quantification, which can be done readily for any patient. We found that, in about the first 200 patients, if you have less than 25% lung involvement, the risk of going to ICU or dying is about 18%. If you have more than 25%, the risk is much higher,' Ohana said.

The risk of fibrosis is also a central concern in these patients. Clinicians know from other types of ARDS – not related to COVID-19 – that 50-75% of patients after ARDS are at risk of fibrosis, with varying severity, whether with radiological lesions or clinical lesions.

'If you have fibrosis on imaging, and even if it is subclinical, it is a risk marker for mortality.

'The question that remains is regarding the risk of fibrosis in COVID-19 survivors, after ARDS. We currently do not know this risk because we have not had enough time after the initial ICU stay,' he explained.

There are different potential evolutions, from ground-glass opacities to crazy paving to consolidation. The questions radiologists must ask themselves are: How can they screen these patients to see which are leading to recovery and which are leading to fibrosis? And when should they follow up with these patients?

'Based on experience with other types of ARDS, we think that less than three months is probably too early for follow-up CT for patients leaving the ICU. And when doing the follow-up scan, we try to optimise the acquisition protocol so as not to have over-radiation,' he concluded.

Pulmonary embolism – An early paper, from Italy, on pulmonary embolism and COVID-19 questioned whether there was a random association between the two. Clinicians now know from a wealth of evidence that it is not random, and there is a strong association between pulmonary embolism, indeed all thrombotic phenomena, and COVID-19, according to Anand Devaraj, a professor of thoracic imaging at Imperial College London's National Heart and Lung Institute. 'A number of publications have shown that the rate of pulmonary embolism in patients undergoing CTPA admitted with COVID-19 is around 30%,' he said. 'There is also evidence to suggest that this is not just a question of pulmonary embolism, but of hypercoagulation in COVID-19 pneumonia.'

The parameters that suggest this phenomenon include, for example, very high D-dimer levels in patients with COVID-19.

'The pulmonary emboli that we see in Covid-19 pneumonia are often segmental or subsegmental. But a significant minority of patients also have quite severe clot burden, more proximally. Some patients also have very elevated right heart pressures and right heart dysfunction.'

The precise treatment and prevention of pulmonary embolism in these patients is a complex decision for clinicians based on a number of factors, taking into account hypercoagulability and the risks of haemorrhage. But there are reports of thrombolysis being effective in patients with large clot burdens and very high D-dimers, according to Devaraj. 'In terms of parenchymal signs, there have been a number of reports describing the observation of dilated subsegmental vessels in patients with COVID-19 – known as vascular thickening, or vascular congestion – seen in up to 89% of patients. We have also seen this in our patients with severe respiratory failure due to COVID-19.'

These dilated subsegmental vessels are peripheral and branching, mimicking tree-in-bud nodularity, but very much centred on the vessel. The aetiology of these opacities is uncertain, but they could reflect thrombotic microangiopathy,' Devaraj noted.

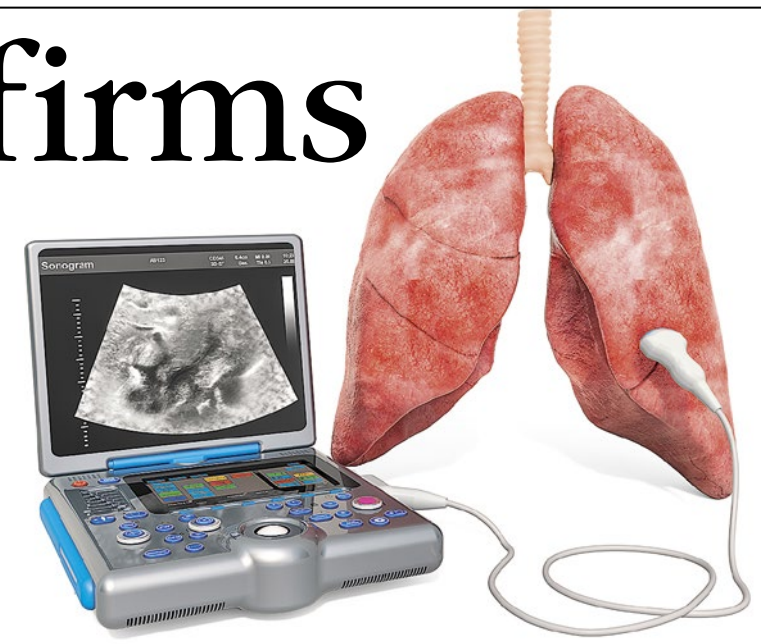
Some recent autopsy data has also pointed towards thrombi within the peripheral vasculature being present as a common phenomenon.

The thrombotic hypercoagulable state that radiologists see on imaging in COVID-19 is not just pulmonary embolism; there are also reports of

Continued on page 14

Epidemic: POCUS hailed as the initial screening tool

Ultrasound confirms frontline value



Ultrasound could become the prime modality in emergency settings for tracking disease progression in Covid-19 patients, Mark Nicholls reports.

While chest CT has held a key diagnostic role thus far, many experts now advocate the benefits of ultrasound within the context of the coronavirus epidemic. Dr Rachel Liu, who recently led a high-profile panel discussion with experts from the USA and areas of Europe with high incidence of COVID-19, discussed the advantages offered by ultrasound, and particularly point-of-care ultrasound (POCUS).

Liu believes the role of POCUS and traditional ultrasound has changed with the length of the pandemic, and will continue to evolve. 'In the early stages of the crisis, lung ultrasound was used diagnostically in conjunction with COVID swab testing, because swab testing could be unreliable,' she explained. 'It may have also been used to aid physicians in selecting the patients most eligible for swab testing.'

However, as the pandemic evolved, and with better testing available, the value of ultrasound as a portable, flexible and time-efficient modality increased, with its value becoming more apparent in categorising mild, moderate or severe disease, discharge decision-making, and baseline monitoring of cardiac function and lung involvement for patients admitted to the hospital, for example.

Liu, who is the emergency ultrasound fellowship director for the Department of Emergency Medicine and the Director of Point-of-Care Ultrasound Education for Yale School of Medicine, said the key seasons ultrasound has emerged as a first liner in emergency settings to diagnose Covid-19 is largely due to avoidance of exposure and transmission of virus particles; disinfection; and preservation of PPE.

'Emergency personnel are often the first to see, examine, and talk to a patient,' she said. 'As we need to see the patient anyway, it makes sense if we perform as complete an evaluation as possible to avoid others needing to come into contact with that patient. This includes obtaining swabs, lab work and imaging. If the emergency provider can perform diagnostic imaging at the same time as evaluating the patient, then this prevents others – transporters, cardiologists, radiologists and technicians – from needing to come into close contact with the patient.'

Cleaning and disinfection

A second critical area is cleaning and disinfection, particularly where CT suites are fixed spaces that would be shared by COVID and non-COVID patients.

'Many hospitals do not have enough machines, or the infrastructure to create cohorted radiology spaces. So, a CT performed on a Covid-positive patient would shut down that machine for up to an hour, so that it, and the surrounding space, can be cleaned. Contrast that with a portable ultrasound machine which can be cleaned and disinfected in a matter of minutes, with a dwell time of only 2-3 minutes between cleaning and use on the next patient.

'Often, and particularly if a site also uses pocket or handheld devices, there is more than one machine in the emergency department. That means that there is a possibility of dedicating machines solely for use in COVID spaces, while also having machines available for non-COVID spaces.'

Thirdly, as fewer people need to come into contact with the patient, less PPE is used, which helps conserve PPE in a time of worldwide shortage.

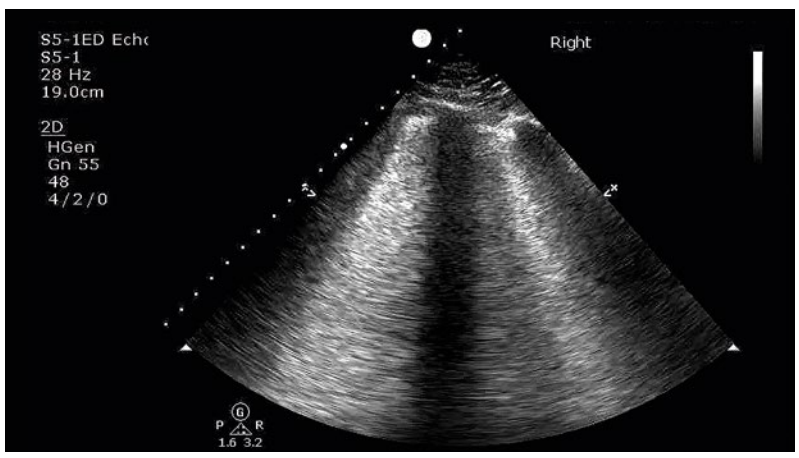
Liu said ultrasound offers advantages over CT, and other modalities, in the coronavirus context and points to preliminary literature in the Covid time period, as well as previous imaging literature on Acute Respiratory Distress Syndrome (ARDS), suggesting that lung ultrasound approaches share similar test characteristics with CT.

With all the advantages of isolation from others, speed of operation and cleaning, Liu concluded POCUS to be overall 'the most expedient modality'. Portable chest X-ray, she added, does not have test characteristics that match CT, and findings on both CT and lung ultrasound can be seen before they appear on X-ray, though she acknowledged that all imaging has limitations.

Five reasons for diagnostic ultrasound

The 10-strong expert panel's discussion report highlighted five reasons why diagnostic ultrasound should be considered for imaging in suspected COVID infection cases: both a normal and abnormal lung ultrasound may provide key clinical insights; lung ultrasound may help rule out other pulmonary diseases; cardiac ultrasound could detect heart problems caused, or exacerbated, by COVID-19; ultrasound may benefit critically ill patients needing peripheral or central venous access; POCUS can reduce numbers of healthcare workers exposed while supplying immediate diagnostic information.

Depicting fluid in the interstitial space that surrounds alveoli with severity causing confluent B lines



We need a global view of Covid-19

Continued from page 13

increased rates of ischaemic stroke, myocardial infarction, and aortic and cardiac thrombus, Devaraj explained.

Neurological complications – COVID-19 can also be responsible for neurological complications, according to Myriam Edjlali-Goujon, a neuroradiologist at Hôpital Raymond-Poincaré, Paris-Saclay University. 'There are two physiopathological mechanisms suggested to explain these complications. The first is using the spread from mechanoreceptors in the lung via a synapse-connected route to the medullary cardiorespiratory centre; the second is entering the brain primarily via the olfactory bulb,' she said.

This second hypothesis has been validated on other types of SARS-CoV virus and was published more than ten years ago. The hypothesis is sustained by clinical symptoms, such as anosmia, which is present in more than 80% of patients with mild-to-moderate forms of COVID-19. 'Anosmia is becoming a very specific symptom of COVID-19, especially when reported without nasal obstruction or rhinorrhea. It is also sustained by imaging publications showing abnormal T2 signals of olfactory bulbs,' she explained.

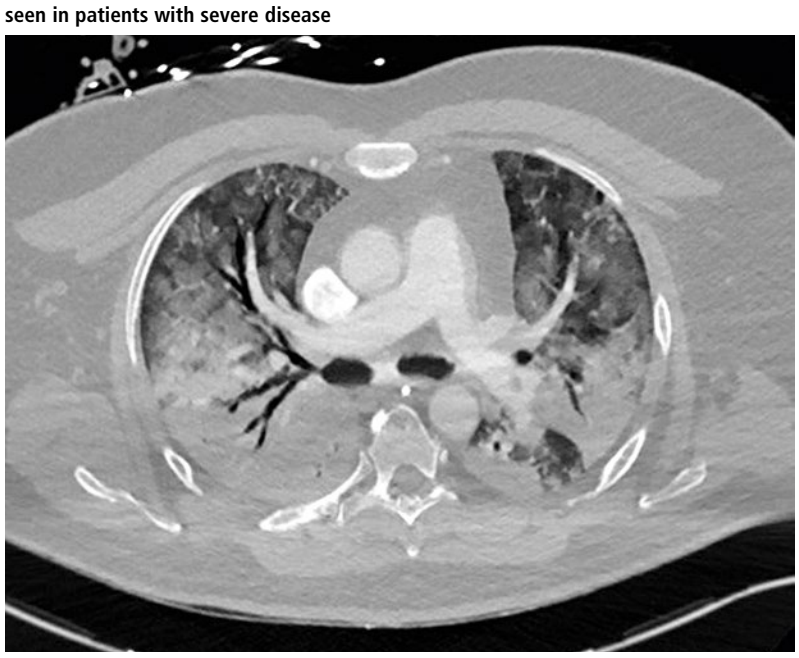
One of the first articles on brain lesions, from March 2020, described acute haemorrhagic necrotising encephalopathy, a well-known post-viral complication, especially of the influenza A virus, in which radiologists see T2/FLAIR hyper intensity within bilateral thalami and temporal lobes, evidence of haemorrhage and enhancing lesions on post-gadolinium sequences.

Cytokine storms – 'Acute haemorrhagic necrotising encephalopathy has therefore been related to intracranial cytokine storms. This is interesting because cytokine storm syndrome has been recently reported in COVID-19 patients and may play a role in the development of those types of encephalopathy,' Edjlali-Goujon noted.

Another example of the polymorphism of the different secondary diseases related to COVID-19 is the aspect of the cytotoxic lesion of the corpus callosum (CLOCC) in a COVID-19-positive patient. There is a presence of an ovoid region of the splenium of the corpus callosum with increased T2/FLAIR signal, high DWI diffusion, with restricted ADC values and reduced T1 signal on post-gadolinium injection.

CLOCC lesions are known to be secondary to an underlying evolving cause and the corpus callosum is very sensitive to markedly increased levels of cytokines. 'Both acute haemorrhagic necrotising encephalopathy and CLOCC therefore suggest specific complications related to maladaptive cytokine profile,' she explained.

Patient with Covid-19 pneumonia: CT shows left lower lobe pulmonary emboli. Dependent dense opacification and anterior ground glass opacities are present in keeping with ARDS. Note also serpiginous dilated peripheral vessels that are frequently seen in patients with severe disease



Different retrospective studies have been published reporting the prevalence of neurological complications. One from Strasbourg and another from Wuhan show that neurological manifestations may occur in 40-70% of hospitalised COVID-19 patients. In terms of neurological signs, agitation was very frequent; and in terms of brain MRI, leptomeningeal enhancements, perfusion abnormalities and cerebral ischaemic stroke have been noticed.

'Most frequently, when a lumbar puncture was done, the RT-PCR for SARS-CoV-2 in CSF was negative. Meanwhile, new reports of rarer complications are emerging, such as Guillain-Barré syndrome, Myelitis, Miller-Fisher syndrome and encephalitis,' she added.

Besides, a study published in the New England Journal of Medicine showed an association between COVID-19 and increased incidence of stroke, because of pro-inflammatory and prothrombotic disease, with emergent large vessel occlusion detected as an early stage or even presenting symptom. However, the studies show that the number of stroke patients decreased within the COVID-19 pandemic, Edjlali-Goujon pointed out. 'In France, there is a 21% decrease of mechanical thrombectomy during the quarantine. But this could be questioned too, because of the significant increase in care delays,' she said.

Anosmia and other abnormalities of the olfactory bulb are usually linked to mild-to-moderate symptoms, often isolated, without other neurological deficits and most often without any other abnormalities on MRI. Apart from anosmia, there are more severe complications, such as maladaptive cytokine profile, leptomeningitis and encephalitis, and hypoxic and thromboembolic lesions. In the second phase of the disease, inflammatory lesions can appear and radiologists have to watch for these very carefully.

'There is a need for a global view on the disease,' Edjlali-Goujon concluded, 'and an epidemiological follow-up; and it is important for the physiopathological hypothesis to be validated on post-mortem studies.'

At Yale School of Medicine, in Connecticut, **Dr Rachel Liu** is the emergency ultrasound fellowship director at the Department of Emergency Medicine and the Director of Point-of-Care Ultrasound Education. Her research interests include the use of point-of-care echo to guide performance of cardiopulmonary resuscitation, integration of new technologies into hospital and educational infrastructure, and system-wide development of point of care ultrasound programs. She has held all major leadership positions within the ultrasound sections of the American Emergency Medicine societies, notably the American College of Emergency Physicians, for whom she authored guidelines for implementation of handheld ultrasound technologies.

'Much is still being developed,' Liu concluded, 'but I think the role of point-of-care ultrasound as an initial screening tool has become more established. Prior publications on ultrasound in H1N1 and ebola patient care already suggested this, but this pandemic has really made this concept hit home.

'This can translate to imaging considerations throughout the length of the pandemic, as well as in future pandemics. Because of this, POCUS should be firmly established in future emergency preparedness and global public health or public policy plans.' Research is underway in developing severity scores based on ultrasound findings, Liu added, and this may help in the second or third waves of COVID, as well as in future pandemics.

A clean slate to design imaging investigations in an ideal world

Out of adversity comes opportunity

The critical role of radiographers in the coronavirus epidemic was highlighted in the final episode of the ESR Connect series of webcasts, 'Radiology fighting Covid-19'.

Three European speakers in the session 'Radiologists & Radiographers: Lessons learned from the pandemic' (chaired by Helmut Prosch, Professor of Radiology at the Medical University Vienna), discussed their coronavirus experiences and how the pandemic might impact on radiology departments in the future – particularly as they work towards regaining routine clinical practice.

Dr Nick Woznitza, senior lecturer and radiographer at Homerton University Hospital and the Canterbury Christ Church University in the UK, detailed the British Society of Thoracic Imaging's Radiology Decision Support Tool for suspected COVID-19 and the route such patients take.

Having been heavily involved in coronavirus care, Woznitza shared his experience in his presentation 'Covid-19 – Departmental Planning & Radiographer Interpretation', summarising how radiographers keep patients and colleagues safe and examining how imaging departments can begin to plan for the post-pandemic.

Dr Nick Woznitza is senior lecturer and radiographer at Homerton University Hospital and the Canterbury Christ Church University in the UK. Radiographer **Dr Moreno Zanardo** is a research fellow at the radiology department of the University of Milan's IRCCS Policlinico San Donato; and **Dr Lukas Ebner** is the leading thoracic radiologist at the Inselspital Berne, Switzerland.

A phased reinstatement of other healthcare services according to clinical need, with pre-screening of outpatients for symptoms, remain key considerations, with dual working, where possible, to help reduce cross contamination, decontamination of equipment/rooms, and streaming into suspected/non-suspected Covid area.

'The key question,' said Woznitza, 'is how we start managing the patient flow in the department and are we "reinstating, or reinventing" healthcare?' One approach in England, he added, has been to adopt a regional approach, using different hospital sites for suspected or non-suspected coronavirus cases.

Radiographers were 'at the forefront of the crisis', he added, playing an essential role in managing the pandemic and triage of Covid-19 cases, emphasising the importance of giving radiographers the right education and support to perform effectively under challenging circumstances. 'Radiography triage will add value; radiographers are often the first healthcare professionals to see a diagnostic image; they have a key role as frontline, patient-facing staff. They deliver good patient management, reduce transmission risk and lead to reports produced as soon as possible.'

In looking at the pathway to go back to normal, he said: 'We do not need to reinstate services; we need to reimagine services; there is the opportunity for a clean slate and start designing imaging investigations along the lines of how we would design them in an ideal world, rather than automatically do everything the same as we have always done. Out of adversity,comes opportunity.'

Radiographer Dr Moreno Zanardo, currently a research fellow in the radiology department at the University of Milan's IRCCS Policlinico San Donato, outlined how workflows can be maintained under difficult conditions, and key areas of minimising Covid-19 infection from patients; training radiographers in protecting themselves; maintaining precautions in the post-pandemic setting; and the role of mobile equipment.

Covering his experiences against a backdrop of limited clinical activity, PPE shortages, and steps towards the transition back to routine practice, Woznitza outlined how his institute minimised the risk of infections using isolated imaging rooms for suspected or confirmed Covid-19 patients; dedicated pathways to perform radiological examinations; centralised PPE supplies and appropriate equipment sanitisation scheduling to limit contamination.

Sharing information – such as the WHO document on how to wear PPE correctly and involvement with an international group to train radiographers in the context of Covid-19 – and considering the mental health of radiographers and preventing burnout, with free psychological support and a weekly survey to investigate potential stress, are also crucial.

Use of mobile X-ray equipment was a valuable step, with the Bergamo region, at the epicentre of the Italian outbreak, performing more than 500 chest X-rays in nursing homes or patients' houses.

'We believe the costs of this approach are lower than bringing the patient to the radiology department,' Zanardo said. 'It also can be useful for reducing contamination and stress for the patient.'

Radiology dose is low; shielding is not mandatory, because lead aprons can be a transmission risk, he pointed out.

Now work must be rescheduled to move towards normal practice but, he noted, there are 1.2 million missed mammographs in Italy with asymptomatic screening mammography on hold until community risk is minimal.

Dr Lukas Ebner, leading thoracic radiologist at the Inselspital Berne, Switzerland, gave an overview of the benefits and disadvantages of CT versus radiography for imaging Covid-19 patients, taking into consideration local healthcare policies, resources and management at the point of care.

CT, Woznitza pointed out, is a sensitive tool, particularly in the early stage of Covid-19 and in patients with no or mild symptoms and in the identification of complications such as pulmonary embolism, whilst chest X-ray is not so sensitive for early findings but with moderate, more advanced or severe symptoms, the 'sensitivity increases substantially', the radiologist adds..

Other factors to consider are the logistics of having to send patients for a CT, the resources, and hygiene measures.

Ebner explained the triaging process at his hospital, which has a fast-track solution offering a turnaround time of two hours to rapidly identify patients who need hospital care and those who can self-isolate at home.

He also highlighted examples of patients seen during the crisis at various stages of their disease progression and follow-up in each modality, along with useful resources helpful to radiologists and radiographers during the current epidemic. These included, 'Covid-19 and the radiology department' from the European Society of Radiology and the European Society of Thoracis Imaging; and 'The Role of Chest Imaging in Patient Management during the Covid-19 Pandemic: A Multinational Consensus Statement from the Fleischner Society'.

Mobile and portable X-ray machines circle the globe

International sales soar

Orders for mobile X-ray solutions made by OR Technology, in Germany, have multiplied several times since the Coronavirus COVID-19 global epidemic began, with orders from Vietnam, Luxembourg, Portugal, South Africa, Ghana and Trinidad & Tobago and many other countries. 'With this X-ray system, the challenges of the pandemic can be mastered better,' confirmed Managing Director Bernd Oehm. 'In a few seconds, excellent pulmonary images of a suspected COVID-19 patient can be obtained. Our lightweight complete solution Amadeo M-DR mini, for example, is suitable for outdoor use as well as bedside imaging in hospitals or nursing homes.'

This advanced all-in-one system includes all necessary components, such as X-ray detector, X-ray generator and image processing station. The user is supported by a practical X-ray assistant. 'The Amadeo M-DR mini enables wireless digital X-rays of the entire body trunk,' the manufacturer adds.

'The X-ray solution is brought directly to the patient, preventing long waiting times in crowded hospitals. The unit can be set up and ready for use in less than two minutes. Transport and operation can be carried out by one person. The integrated diagnostic software ensures a worldwide and fast exchange of information via cloud or e-mail. This saves a lot of time and transport costs,' OR Technology points out. 'In the case of a temporary power interruption, the device can still be used to take X-ray images.

'The compact X-ray unit is simple and easy to move,' OR adds. 'Folded up, it's easy to transport and even fits into a station wagon. Steps and uneven terrain are no obstacle. The wheels allow easy 360-degree rotation even when folded, which makes it much easier to handle in confined spaces such as elevators.

Details: info@or-technology.com


Mobile X-ray machine Amadeo M mini for ambulatory and in-patient care

Radiographers on the front line

Prioritising equipment hygiene

The pandemic has put extra pressure on radiology services and radiographers are particularly at risk of catching and spreading the disease. Strict cleaning and disinfection protocols must be followed, according to Pablo Valdés Solís, President of the Spanish Society of Radiology (SERAM), who recently published new guidelines on how to protect staff and patients.

Report: Mélisande Rouger

Ever since the first COVID-19 cases were reported in January, radiology workflow changed entirely and the focus fell on an essential, yet not visible, part of the department's work: equipment hygiene. 'Increasing awareness of how to clean and disinfect devices adequately is crucial not only to protect our staff, but also not to spread the disease to patients and colleagues during radiology examinations,' cautioned radiologist and President of SERAM, Pablo Valdés Solis.

A new resource to support radiographers: basic concepts of Covid-19

The SERAM published guidelines last April to help radiographers keep staff and patients safe during the pandemic, because the Spanish radiographer training doesn't include the necessary microbiology background to understand how the disease spreads.

'Radiographers don't receive that much training in virology. But if you understand what the disease is and how it spreads, you will better understand what needs to be done,' Valdés said.

The document reviews basic concepts of COVID-19 and suggests a detailed list of measures that must be taken in radiology departments to prevent its spread during radiological examinations.

It has been observed that the virus can survive as long as three days on stainless steel and plastic. Staff must therefore not only wash their hands before, during and after an examination, but also clean and disinfect all the equipment they have used with a patient.

Keeping equipment intact means that all surfaces that will be in direct contact with a patient should be covered as much as possible with impermeable material that can be discarded after each examination.

For example, in portable X-ray, radiographers should cover the shell with a plastic bag. In ultrasound, it is preferable to use a sleeve to cover the probe, but not absolutely necessary if the patient's skin is clean.

'If you have sleeves, you should cover the equipment and especially the console area, to facilitate posterior disinfection and minimise damage risk to the equipment,' Valdés pointed out.. The equipment can be washed directly with soap and water or specific cleansers. Powerful cleansers, organic disinfectants, alcohol and dissolvent should never be used as they may damage the surface.

Disinfection is another key step of the cleaning routine, especially during the pandemic. The aim is to diminish the microorganism load, assuming that some will remain in non-threatening levels.

Disinfection can be classified into three levels. The so-called low level is the elimination of bacteria, fungus and some viruses by applying the product in the examination room and on the equipment surface for less than ten minutes.

Intermediate-level disinfection consists of eliminating TB bacillus and most of the existing bacteria, viruses and fungus. High-level disinfection is the complete elimination of germs – except bacterial spores – and is traditionally used to decontaminate medical devices, such as endoscopes, anaesthetic material and other medical devices that have been in touch with a patient's mucosa.

Sterilisation will eliminate all microorganisms, including bacterial spores, from any surface in critical material like endocavity probes, surgical material and non-reusable interventional material.

The coronavirus is covered by a lipid layer and is therefore vulnerable to soap and traditional disinfectants. For most medical equipment used in daily routine, low to intermediate disinfection is enough. Special products are not necessary and the disinfectant solution can be applied for five minutes. For example, a solution made of 0.1% sodium hypochlorite (bleach), 62-71% ethanol or 0.5% hydrogene peroxyde can inactivate the virus in just a minute.

The solution should not be applied directly though, but by using a gauze, compress or cloth that has been previously soaked.

Different areas throughout the country need different protocols

Hospitals across Spain are affected differently depending on the local incidence of the COVID-19 coronavirus. Madrid has been the most impacted area, with 68,852 infected patients as of June 1, according to the Spanish Ministry of Health.

The Spanish capital has derived COVID-19 patients to major institutions like La Paz and Ramon y Cajal, and temporary structures like IFEMA, a conference centre that has become Spain's largest hospital with 5,500 beds.

By comparison, Andalusia has registered 12,679 infected patients, 134 of these in the past 14 days.

Due to these differences, hospitals must themselves decide which hygiene protocols they need to follow. 'We recommend establishing these rules together with the local preventive medicine experts. Taking care of the examination rooms and materials starts by adequate cleaning, according to the hospital policy,' Valdés pointed out.

Also important to bear in mind are the protocols recommended by equipment manufacturers, as some devices or components may be more sensitive, for instance ultrasound probes and some areas in CT gantries.

The unexpected positive consequences for simple X-ray exams

Radiology is learning lessons from the pandemic, Valdés observed. 'We've regained an excellent habit, which is to report on simple X-ray examinations. This is really something we need to value more. Being able to study simple radiology is extremely important.'

Keeping equipment clean has also returned to centre stage. 'Radiation and magnetic resonance safety have long been the focus of our preoccupations, but it's very important to take care of the material as well,' the SERAM President concluded. Infectious diseases are traditionally the concern of clinicians, but this pandemic has reminded us of how important hygiene is and that we all have a role to play.'

Pablo Valdés Solís is Area Director of Costa del Sol Healthcare Agency in Marbella, Malaga, Spain, and the current President of the Spanish Society of Radiology (SERAM), and has over 25 years professional experience. His special interest lies in paediatric radiology and emergency radiology. For the past fifteen years, he has focused on management and quality.

The need for modernisation

Digital pathology: Luxury or necessity?

The anatomical pathologist faces a crisis. Public and private labs suffer increasing caseloads, whilst pathologist numbers diminish for various reasons, including greater cancer prevalence associated with aging populations as well as improved cancer screening programs. Precision medicine typically involves more genetic testing and extensive use of immunohistochemistry to classify cancer and assess prognostic and predictive biomarkers.

In clinical practice, a notable number of pathologists are nearing retirement, yet today's diagnostic pathology training of young doctors is limited.

Alternative: the optical microscope

Recently, digitisation and digital pathology have become widely accepted due to advances in technology and regulations. In essence, in digital pathology a scanner produces a digital copy of the traditional glass slide, to be stored in a local or cloud-based server and viewed anywhere with a computer and internet connection. Current scanners provide high fidelity digital images thanks to high magnification (40x). Additionally, high throughput scanners, with a capacity of up to a thousand slides, are capable of fast, reliable operation with little human intervention, making possible unsupervised overnight operation and samples ready for review by pathologists and trainees in early morning.

Licensed but a slow uptake

In 2017, the USA's Food and Drug Administration (FDA) warranted the first license for the use of digital pathology for primary diagnosis in that country. Permission for in vitro diagnosis came sooner in Europe.

Despite this, adoption of digital pathology has been slow for several possible reasons. A commonly mentioned barrier is pathologists' concerns, such as digital images inferiority, or a slowdown in the sign-out process.

Decades ago, when digitisation entered radiology to produce digital images, film was no longer needed. The savings eased an initial reluctance among some groups, but not in pathology since elaboration of the glass slide is still required. This, coupled with concerns over increased turnaround times due to the added step of scanning, as well as the substantial initial investment needed to fully digitise a lab, help explain the slow rate of path digitisation.

What's in it for pathologists?

Despite concerns, today's digitisation brings multiple advantages to pathologists and patients. Early digital pathology adopters report many benefits, including efficiency gains and better case allocation across digital pathology networks. The availability of a digital histology slide enables distant viewing and remote reporting, particularly appealing given demands imposed by COVID-19. Multiple users can access digital images, regardless of location, enabling second opinions and consultations. Shipping and storing glass slides on site is obviated.

Digital rather than analogue archives are more manageable; prior cases are available quicker for comparative review.

Early users report overall efficiency includes shorter reading times during diagnostic sign-out sessions, improved overall lab efficiency in the range of 20%, or more, after complete digital diagnosis, compared with analogue workflow.

In addition, the improved intra-laboratory logistics (the technician time required to sort the hundreds of slides prepared every day in the typical lab, distributing them to the responsible pathologist, collating them for tumour boards, and the added ease to manage consultations, etc.) may add to the savings and lower the financial barriers for adoption.

Artificial intelligence in pathology – friend or foe?

Artificial intelligence (AI) tools, including deep learning algorithms, can be applied to a digital histology image to facilitate computer-assisted diagnosis, which forms the basis of computational pathology. The application of AI to pathology bears promise, including increased accuracy in immunomarker quantification, better sample screening and pathologist efficiency, with reduced mis-diagnoses.

The discovery of new morphological predictors of disease outcome, invisible to the human eye but apparent to a computer, also suggests new diagnostic possibilities. The current capability to manage and analyse huge pathology image data, combined with more advanced techniques to simultaneously detect multiple molecules or antigens *in situ*, fosters a novel field of research. However, a prerequisite for computational pathology to fulfil its promises and become mainstream, is the general adoption of digital pathology – because the development and training of AI algorithms requires vast amounts of carefully annotated digital data. Additionally, once algorithms have been developed, they can only be applied in clinical routine use in labs that have successfully embraced digitization: by logic, AI tools cannot be applied to analogue glass slides.

Some medical professionals fear that machines could work more rapidly and accurately than a human. However, the whole point of computer assisted diagnosis and computational pathology is to help pathologists.

In monetary terms

Digital pathology efficiency gains can be translated into monetary terms. It is important to estimate how long before an initial investment in lab digitisation show a return. A model proposed by the University of Leeds, in the UK, estimates that efficiency gains of between 10-15% result in an amortisation of the initial investment after 1-2 years. Based on this model, efficiency gains of 20%, as reported by some users, would point towards an early amortisation of the initial cost outlay.

How staff requirements change due to enhanced productivity in a fully digital lab needs analysis. Where pathologists are retiring and cannot be replaced, early digital pathology adopters report that, due to greater efficiency, a reduced pool of pathologists can absorb increasing caseloads. The differences in full-time equivalents (FTEs) of pathologists' time to process the same caseload, when comparing those on the microscope, versus that same group of pathologists with better efficiency after digital transformation, show that the personnel savings from fewer FTEs needed are sufficient to amortise the initial investment after 2-3 years. Additionally, these FTEs savings, over five years – the typical life of a digital pathology system – do result in an additional lab profit over the fourth and fifth year, before additional expenditure is needed to renovate obsolete elements in the system. Therefore, the investment made efficiency gains that translate into a repayment of the initial amount around the second year and additional monetary gains for a further 2-3 years.

Can I work remotely?

A pillar of digital pathology is reliance on the creation of a digital twin of the glass slide, in a file accessed by anyone with the appropriate credentials from anywhere with an internet connection and a PC. The images are typically stored in a server, usually integrated within the main hospital infrastructure. From here, the digital slides can be accessed remotely via a virtual private network (VPN), that creates a secure access to the hospital IT system. The data transmission rate necessary for satisfactory viewing – a bandwidth of 300 megabits per second (Mbps) – is sufficient to ensure optimal performance when loading, panning and zooming the image. Currently, the typical optic fibre bandwidth for domestic use offers three times that speed.

Other important elements are the PC and monitor needed to view digital images. In 2017, the FDA warranted permission to the first digital pathology system for primary diagnostic use in the USA. Part of the system is a PC with an Intel Xeon CPU E5-1620 v3 at 3.50-GHz processor, 16 GB RAM, and an NVIDIA Quadro K4200 graphic card. These hardware elements, as usually with IT components, cost significantly less now. The FDA monitor approved for primary diagnosis is medical grade LED with a resolution of 1920x1200 pixels and a self-calibration mechanism. However, the emergency declared due to COVID-19 has resulted in a temporary relaxation of regulations pertaining domestic reporting, and currently user discretion is recommended when using domestic PC and monitors for home reporting.

In short, the IT infrastructure needed for remote diagnosis is not unduly demanding and can reasonably be met even by domestic users, which makes home reporting possible – particularly interesting in terms of social distancing rules due to the Covid-19 pandemic.

Dr Juan Antonio Retamero is an anatomical pathologist with extensive experience in the implementation and use of digital pathology for routine diagnosis. He played a key role in the adoption of digital pathology in a pioneering group of Spanish hospitals in 2016. He has shared those experiences internationally and supported many centres in adoption digital pathology adoption globally, including labs in the USA. Europe and Asia. He is a regular speaker at digital and computational events and an ardent advocate for modernisation of the profession. Retamero is also Consultant for Philips Digital and Computational Pathology.

Falko Fend MD is Professor of Pathology and Chairman of the Institute of Pathology and Neuropathology and Reference Centre for Haematopathology at the Eberhard-Karls University in Tübingen, Germany. Following postgrad training in the Pathology and Internal Medicine Departments at Innsbruck University, in 1991 he became its staff pathologist. From 1997-1999, he was a research fellow at the Laboratory at the National Cancer Institute, NIH, Bethesda from 1997-1999, when he became Associate Professor of Pathology at the Institute of Pathology of the Technical University Munich, and later took on his current position at the University of Tübingen. His research focuses on the pathology and molecular genetics of malignant lymphomas and innovative molecular pathology.
Fend is also a member of the executive boards of the German Society of Pathology, the European Association of Haematopathology and served as Chairman of the European Bone Marrow Working Group.

The door to simple, cheap, reliable bio-stratification

A more integrative appro

Bringing molecular and digital pathology closer together through a more integrative approach can lead to clear advantages for diagnostic and research workflows, Mark Nicholls reports

During the recent Digital Pathology and AI Congress (London) and in his keynote presentation 'Molecular and digital pathology - the value of an integrative approach', Professor Viktor Koelzer explored the benefits and paid particular attention to colorectal cancer (CRC) during the event. 'It's an exciting time in pathology as we better connect tissue morphology and molecular changes using digital pathology and artificial intelligence,' he told delegates.

Koelzer, who is Attending Pathologist and Assistant Professor at the Institute of Pathology and Molecular Pathology at University of Zurich and University Hospital Zurich, explored recent paradigm changes in clinical diagnostics and research workflows with the potential of predicting molecular features from image data. 'Information from surgical pathology feeds into molecular testing, but we rarely make the loop back. Today we are starting to close this gap,' said Koelzer.

Looking at tumour annotation for molecular analysis, he said challenging areas include the limited reproducibility of visual pathology review, inconsistency with bioinformatic prediction of tumour cell content using sequencing data and the resulting limited correlation of standard pathology assessment with DNA and RNA yield from clinical samples. As the ability to detect somatic variants in cancer samples drives personalised therapy, better tissue classification strategies could help to improve clinical diagnostic workflows.

'An area of development is tissue segmentation by supervised machine learning for the estimation of tumour cell percentage by digital pathology,' he said. This approach allows correlation between different levels of information and provides accurate area information for each tissue component on a given histology slide.

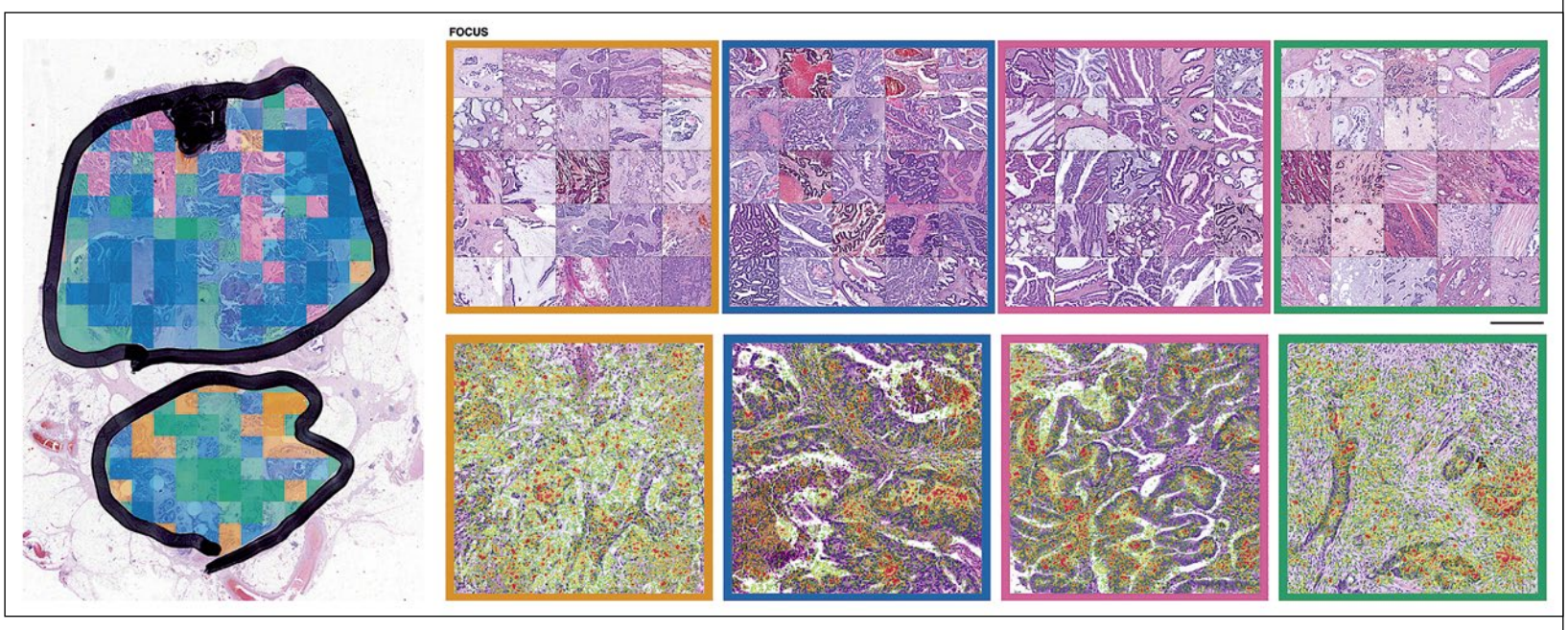


Image-based consensus molecular subtype classification (imCMS) and morphological interpretation with tissue level features

Excellent reproducibility

'It allows us to look at the cell-level composition of histology slides at great detail and with excellent reproducibility," he added, "we can thereby gain additional information from pathology review in an automated fashion that would otherwise be very laborious to obtain.'

Indeed, initial data showed that tissue composition analysis with DNN (deep neural networks) allows analytical robustness, automatisation and standardisation and provides high reproducibility at single cell resolution.

DNA-based tumour purity estimates are more accurate than visual view or deconvolution from genome-wide omic platforms which, he said, tend to under- as well as over-estimate tumour purity respectively. Therefore, digital pathology review using DNN could be used to inform downstream molecular analyses better and investigate tissue-based metrics as potential biomarkers in clinical trials.

CRC has significant potential and is a current area of focus for his research team at USZ in collaboration with Professor Jens Rittscher and Professor Tim Maughan at the University of Oxford.

As part of the CRUK and MRC

Infrared spectroscopy as a diagnostic tool

New techniques of infrared-based technology are showing strong potential for cost-effective tissue analysis, Mark Nicholls reports.

Peter Gardner, Professor of Analytical and Biomedical Spectroscopy at the University of Manchester, outlined how hyperspectral imaging coupled with sophisticated computer algorithms can identify and grade cancerous tissue, as well as offer an indication of prognosis.

The technique, Gardner said, speaking at the 6th Digital Pathology and AI Congress in London last December, lends itself to automation and would be particularly useful to screen large numbers of biopsy samples for common cancers, such as prostate cancer.

Posing the question 'Infrared spectral pathology – an academic exercise or a new diagnostic tool?', he explained that infrared micro-spectroscopy uses an array detector with the image of the sample focused onto an array of MCT (Mercury Cadmium Telluride) detectors, so that spectra from each point on the sample can be obtained simultaneously.

'All tissue contains molecules that vibrate, particularly if you shine infrared light through them,' explained Gardner. The infrared light is absorbed and if we measure this, we obtain an absorption spectrum. Because we have thousands of pixels in our image, we have thousands of spectra and this makes up our data.'

Peter Gardner is Professor of Analytical and Biomedical Spectroscopy and a fellow of the Royal Society of Chemistry at the University of Manchester. He heads a successful biomedical spectroscopy group that focuses on the development of vibrational spectroscopy methods for use in pathology and has demonstrated the utility of the technique for both prostate and breast cancer samples.

Reducing error rates

Focusing on prostate cancer, the team liaised with pathologists over the technique with feedback suggesting that pre-screening with infrared micro-spectroscopy would help focus on the most important cases and that automated pre or post screening of biopsy samples could reduce error rates.

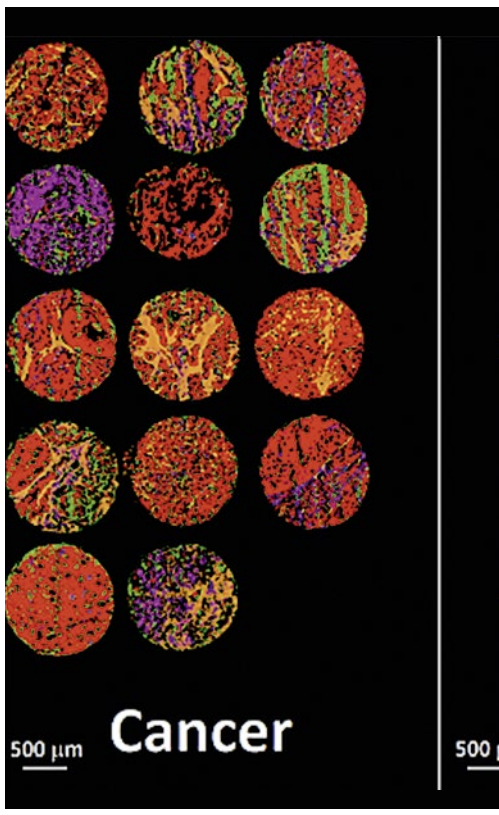
However, Gardner stressed, 'If looking at tissue with infrared spectroscopy, we cannot pin down individual proteins – this is not mass spectrometry – but we can get a spectroscopic fingerprint that might be indicative of something in the tissue.

'The question is, is the fingerprint different enough to say something about that tissue? We can get spectral evidence of that tissue and the image has evidence of the peaks in that tissue – we can see the protein peak, for example.'

The professor acknowledged that spatial resolution is an issue – the best is about five microns – simply because the wavelength of light is longer than visible light, but the research team believe this is still enough to obtain key spectroscopic information.

With no need for stains or dyes, he said, grading for cancer can be shown as well as prognostic information. 'For a two-band criterion looking at stages T1 and T2 against T3 and T4, we can obtain sensitivities and specificities of 91% and 93% respectively,' he added.

He also outlined how spectral information reveals primary tumour behaviour and whether it is invading surrounding tissue. Infrared identification of the tissue pathology highlighted the epithelium, smooth muscle, lymphocytes, blood, extracellular matrix, concretion and



fibrous stroma.

With 2.5 million spectra processed and classified in less than sixty seconds with no staining needed, or de-waxing of the sample, a drawback is the requirement for infrared transparent substrates for pristine results.

Despite this, the research team has shown that reasonable results and diagnostic information could be obtained using standard 1mm glass slides just from the region of spectrum using epithelial pixels. Furthermore, the researchers showed that 'reasonably good' classifications of stroma and epithelium could be obtained directly from heavily H&E stained tissue.

Gardner – who believes the tech-

ach

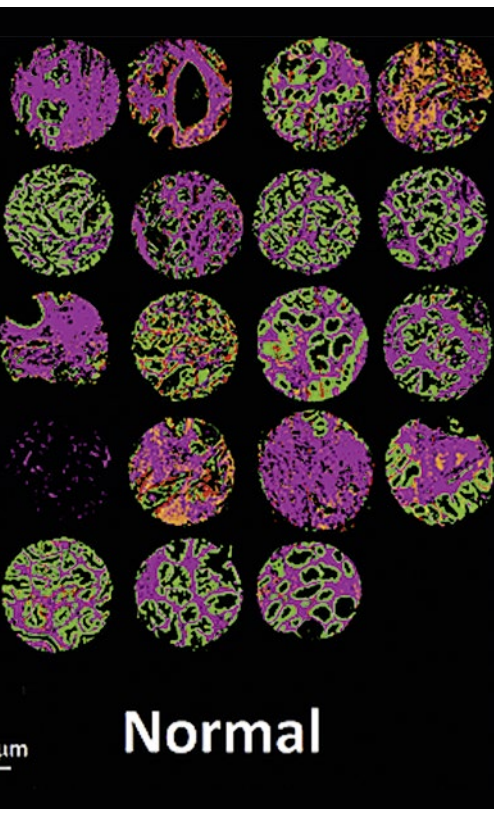
funded Stratification in Colorectal Cancer or S:CORT consortium (www.scort.org.uk), they have previously developed a cheaper, faster method of cancer classification using artificial intelligence to analyse high-resolution images of histological slides. This allows the subclassification of colorectal tumours into one of four distinct consensus molecular subtypes (CMS) and gives an indication of optimal treatment strategies.

As histological grading is a poor predictor of disease progression, and CMS cannot be distinguished without gene expression profiling, a clinical need results for better prognostic/predictive indicators for the disease. 'Clinical stratification using molecular data requires sequencing of tissue samples, which is costly and requires the availability of the relevant infrastructure and bioinformatics resource,' he added, explaining that image analysis can be a cost-effective solution to interrogate morphological features as a surrogate for genetic/molecular information.

Biological understanding of CRC

'We show that image-based CMS (imCMS) of CRC can assess clinical impact, produce a molecular profile and phenotype information for molecular subtypes of CRC. Using this information could improve our biological understanding of CRC potentially leading to better clinical stratification and treatment decisions, such as performing a surgical resection or giving adjuvant chemotherapy.

In conclusion Professor Koelzer said that Computational models can predict transcriptional subtype of CRC from standard histology sections. 'imCMS makes sequencing information interpretable through association of morphology, molecular features and outcome data and classifies samples previously unclassifiable by RNA expression profiling.' It also gives a novel insight into tumour heterogeneity, is highly prognostic; and classifies endoscopic biopsies and resection specimens of CRC enabling patient stratification in diverse clinical settings. Koelzer sees a promising outlook with a better integrative approach for molecular and digital pathology: 'Molecular classifiers can be recognised and called from H&E images, opening the door to simple, cheap and reliable biological stratification within routine workflows and existing retrospective cohorts.'



False colour image of the classified prostate tissue cores based on their infrared spectra:
Red = malignant epithelium,
Orange = cancer associated stroma,
Green = normal epithelium,
Purple = normal stroma.

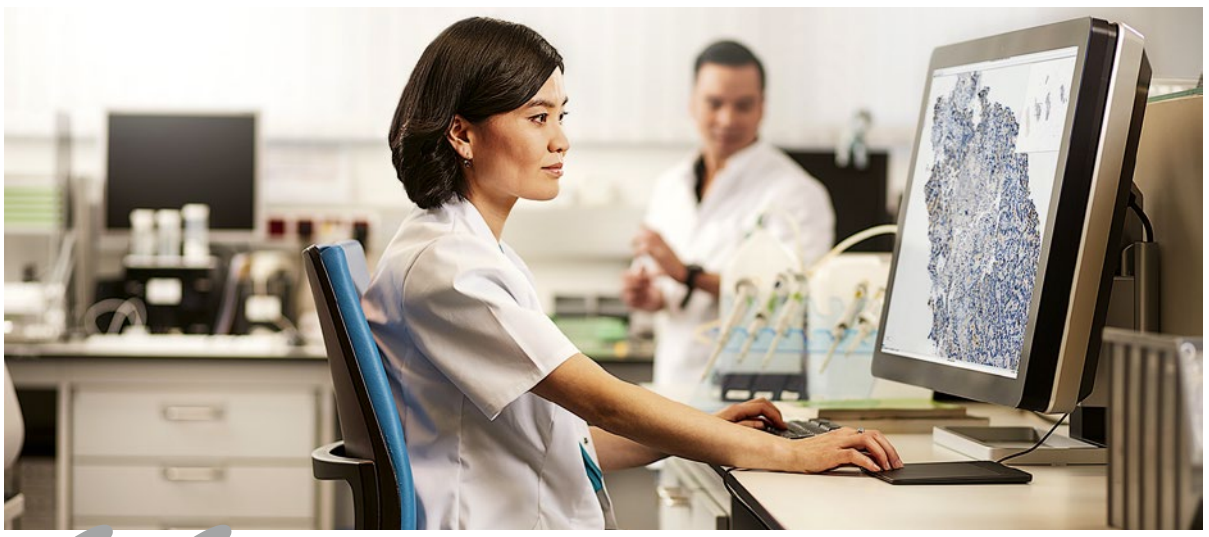
nology is almost ready for clinical translation – concluded: 'Infrared spectral pathology can be used to analyse tissue and provide diagnostically useful information.

'A preliminary study shows H&E gives enough information to provide initial screening and extremes of staining make no significant difference, though the type of glass does, although that can be standardised, Gardner added.'

Viktor Koelzer is Assistant Professor at the Institute of Pathology and Molecular Pathology at University Hospital Zurich and Honorary Senior Clinical Researcher at the University of Oxford. He is passionate about technology in application to daily diagnostic practice and research, in particular improving patient care through the implementation of high-quality, science-driven computational image analysis approaches with a focus on gastrointestinal disease and tumour immunology.

'We need to put our heads together and exchange ideas'

Digitising pathology – one step further



For more than 30 years, Barco has invested significantly in research and development specific to improving workflow and clinical outcomes for healthcare professionals. Barco researchers work closely with clinicians to obtain a deep understanding of the clinical challenges and workflow realities so that they can incorporate this knowledge while developing innovative ideas for tomorrow's healthcare products.

Toward this goal, Barco has developed display systems and technologies designed to empower clinicians to work more efficiently and diagnose more accurately to meet the demand of a growing workload in an era of unprecedented healthcare service delivery.

Digital pathology is sweeping the globe, adding the convenience of bright displays, sophisticated software, and digital archives to the mature histopathology process.

Ultimate slide-to-eye confidence

Digital images are stable over time and can be quickly transported over computer networks to bring the best people and the best images together to improve patient care. Countries vary in their uptake of this new technology, and in the United States of America, the FDA has cleared digital products only for a select subset of IHC applications.

Cédric Marchessoux, research engineer at Barco, explains: 'A lot of challenges need to be addressed before digital pathology can hit the market. First of all, the images are huge, requiring very high resolution imaging devices. Moreover, analysing pathology images is a complex practice and exchanging samples or slides between labs is difficult, which prevents effective collaboration. That's why we need to put our heads together and exchange ideas so we can take the digitisation of pathology one step further.'

What people love about Barco pathology displays:

- Fast viewing, panning and zooming in on digital slides with the powerful Barco display controllers
- Intervention-free colour calibration and record-keeping with Medical QAWeb
- See more details on your slides with a variety of large, bright Barco display models
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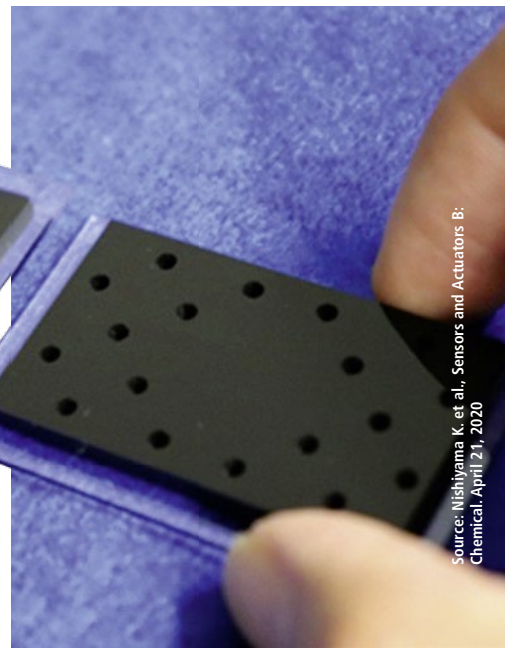
COVID-19

Fast detection of virus antibodies

Researchers at Hokkaido University have succeeded in detecting anti-avian influenza virus antibody in blood serum within 20 minutes, using a portable analyser they have developed to conduct rapid on-site bio tests.



The microfluidic device to which ~20 µL of samples containing 2 µL of serum will be applied

Source: Nishiyama K. et al., Sensors and Actuators B: Chemical. April 21, 2020

If a suitable reagent is developed, a new portable analyser could be used to detect antibodies against SARS-CoV-2, the causative virus of COVID-19. Avian influenza is a poultry disease caused by influenza A virus infection. Rapid initial response for a suspected infection and continuous surveillance are essential to mitigate the damage from highly pathogenic, transmittable pathogens such as avian influenza viruses.

The group, including Keine Nishiyama, a PhD student at Hokkaido University's Graduate School of Chemical Science and Engineering, and Professor Manabu Tokeshi of the university's Faculty of Engineering, conducted this study to develop a new method and analyser capable of rapid, facile and selective detection of antibodies. The method is based on conventional fluorescence polarization immunoassay (FPIA) but applies a different measurement mechanism to make the analyser much smaller and portable. The analyaer weighs only 5.5 kilograms.

Simultaneous examination of multiple samples

The combined use of liquid crystal molecules, an image sensor and the microfluidic device makes it possible to simultaneously examine multiple samples and reduces the volume of each sample required. Liquid crystal molecules are capable of controlling the polarisation direction of fluorescent light, while the microfluidic device has a number of microchannels as a measurement vessel. The group also developed a reagent to detect anti-H5 avian influenza virus antibody, a fluorescein-labelled protein that binds only with the antibody. The reagent was made by reproducing hemagglutinin (HA) protein fragments, which are expressed on the surface of H5 avian influenza virus, through gene recombination and by labelling fluorescent molecules to the fragments.

To make the measurement, serum collected from birds was mixed with the reagent and left for 15 minutes. The mixture was injected into the microfluidic device and measured with the portable fluorescence polarisation analyser. Molecular movements of the reagent bound with the antibody will be smaller in the liquid, producing a different degree of polarisation from the reagent not bound with the antibody. The system can detect anti-H5 avian influenza virus antibody with only two microlitres of serum sample and within 20 minutes. 'Our analyser could be used to conduct other bio tests,' Tokeshi said, 'if suitable reagents are developed.'