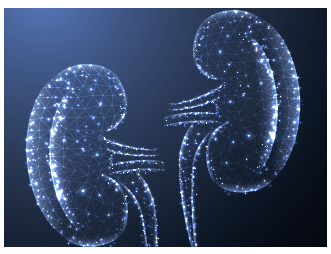
VOL 30 ISSUE 4/21 • November 2021

EUROPEAN HOSPITAL

THE EUROPEAN FORUM FOR THOSE IN THE BUSINESS OF MAKING HEALTHCARE WORK



Prostate cancer: Over-detection and biopsies

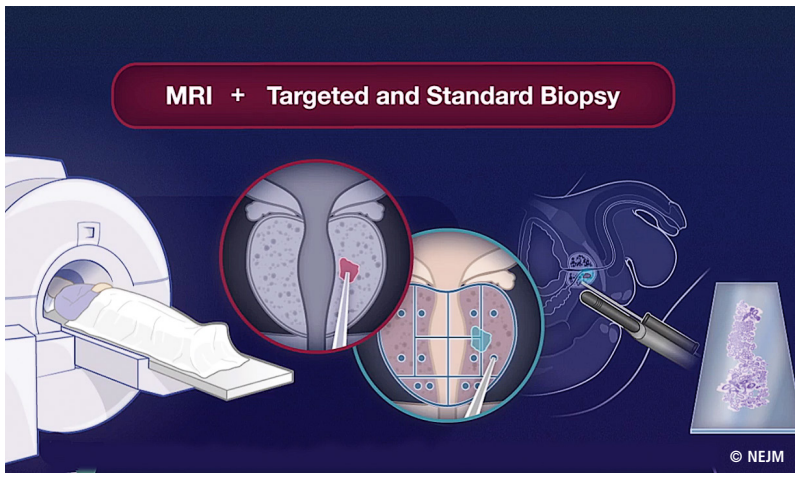
Organised screening enabling early detection and treatment of prostate cancer can reduce death by an impressive 20%, based on 16 years of findings of over 160,000 men participating in the landmark European Randomised Study of Screening for Prostate Cancer (ERSPC). However, the screening process is responsible for overdiagnosis and excessive biopsies of low-grade prostate cancer, and the WHO does not recommend systematic screening, citing a 'high harm/benefit ratio'.

Report: Cynthia E. Keen

Important findings from a randomised clinical study of 12,750 men living in Stockholm County, Sweden, reported this summer at the European Association of Urology annual congress, may change this. Researchers from Karolinska Institute in Stockholm reported that MRI-guided biopsies can reduce overdiagnosis by half compared to traditional ultrasound-guided biopsies. The additional use of a novel blood test -- the Stockholm3 test (A3P Biomedical AB, Stockholm) -- reduced the number of MRIs performed by 36%, while further preventing the need to biopsy minor, low-risk tumours by 8%.

'Our results show that we have identified the tools needed to carry out effective and safe screening for prostate cancer,' said Tobias Nordström MD PhD, principal investigator of the STHLM3MRI study. 'After many years of debate and research, it feels fantastic to be able to present knowledge that can improve healthcare for men.'

Prostate cancer is the third highest cause of cancer deaths in the European Union, with an estimated 78,800 men having died in 2020. Globally, it is the sixth leading cause of cancer death among men, with an estimated 359,000 deaths in 2018 based on the GLOBOCAN database, and is estimated to increase to 740,000 deaths by 2040 due to an aging population.



MRI + targeted and standard biopsy is noninferior to standard biopsy to detect clinically significant prostate cancer. The result is fewer unnecessary biopsies and clinically insignificant cancer diagnoses.

The clinical study

For the clinical study, 49,118 men aged 50-74 living in Stockholm County were randomly selected and invited to participate in a prostate cancer screening to identify whether they were at elevated risk of developing prostate cancer. Between 2018 and 2020,12,750 accepted and provided blood specimens; 2,293 with elevated risk as assessed by PSA and the Stockholm3 test were randomly assigned to either a group who had traditional biopsies performed or a group having a MRI exam followed by a targeted biopsy approach in men with visible lesions on the MRI.

The Stockholm3 test uses an algorithm to analyse a combination of protein markers, genetic markers, and clinical data. Specifically, it determines the concentration of five plasma markers in a blood sample and analyses approximately 100 genetic variants. The results of the analysis are integrated into an algorithm that includes the patient's age, family history, and the result of a previous biopsy, if any. This creates a risk percentage score that a prostate biopsy will have a Gleason score of 7 or greater.

'The combination of improved risk prediction and MRI-targeted biopsy has the potential to establish a new framework for prostate cancer screening,' the researchers said.

The use of MRI-guided and targeted biopsies proved as effective as standard biopsies. MRI can be used to discriminate the need for a biopsy based on the presence/absence of suspicious lesions, and then to target biopsies to those lesions. The researchers said that, in a population of 10,000 men with elevated PSA levels, the MRI approach would result in 409 fewer men having a biopsy, 366 fewer biopsies with benign findings, and 88 fewer clinically insignificant cancers detected than with the standard biopsy approach.

'Our clinical study showed that the Stockholm3 test can significantly reduce the number of MRI biopsies, without compromising the diagnostic capacity of medium grade prostate cancers, in comparison with the use of the PSA value 3 ng/mL as the cut-off value for biopsy recommendation,' they said. Professor Hendrick Van Poppel, Adjunct Secretary General of the EAU, commented, 'It's exciting to see breakthroughs such as this in the field of early detection of prostate cancer. An innovation such as the STHLM3MRI study makes an even more compelling case for the European Commission to ensure that a risk-stratified approach to early detection of prostate cancer is adopted across the whole of Europe. The EAU is working hard to ensure that early detection is addressed in the implementation of Europe's Beating Cancer Plan in order to reduce mortality of Europe's most common male cancer while also dealing with the challenges of overdiagnosis and overtreatment.'

The researchers are currently performing cost-effectiveness analyses using data from the clinical trial. The Stockholm3 test is currently available in Sweden, Finland, Norway and Denmark.


© Danderyds Hospital, Stockholm, Sweden

Associate Professor of Urology at the Department of Clinical Sciences at Danderyd Hospital at Karolinska Institute, **Tobias Nordström MD PhD** combines clinical surgical practice with independent research. The latter focuses on development and implementing improvements in clinical care, such as targeted prostate biopsies and imaging and developing improved guidelines for treatment.

Europe: The pandemic impact on lung cancer care

Covid-19 repercussions

The impact of the coronavirus pandemic on lung cancer patient care across Europe and the contribution of lung pathologists have led to a better understanding of Covid-19, as outlined during the 33rd European Congress of Pathology, Mark Nicholls reports

Within 'The lung pathologist in the Covid-19 pandemic' session speakers detailed how the pandemic has affected patients, diagnosis and clinical trials, yet also highlighted the changes pathologists had noted and detailed in lung characteristics as the pandemic progressed. This, they said, contributed to a better understanding of Covid-19 and helped to shape the response.

Lung cancer in the Covid-19 pandemic

In his presentation, Professor Paul Hofman – who had examined the reasons for the decrease in management of lung cancer patients and consequences of the Covid-19 pandemic for thoracic pathology laboratories in Europe – said patients with lung cancer avoided hospitals because they feared being infected with SARS-Cov-2 and how it would affect their condition.

Care of lung cancer patients was also delayed when appointments and treatment programmes were cancelled. 'These patients were not treated adequately due to extensive devotion of many physicians to Covid-19 patients,' Hofman pointed out. 'Staff members from pathology laboratories were reoriented to work in emergency clinical departments to take part in different activities against Covid-19.'

This resulted in a decrease in molecular analyses in lung cancer during the different waves of the pandemic, particularly in the molecular pathology analyses for genomic alteration assessment in lung cancer.

Continued on page 2

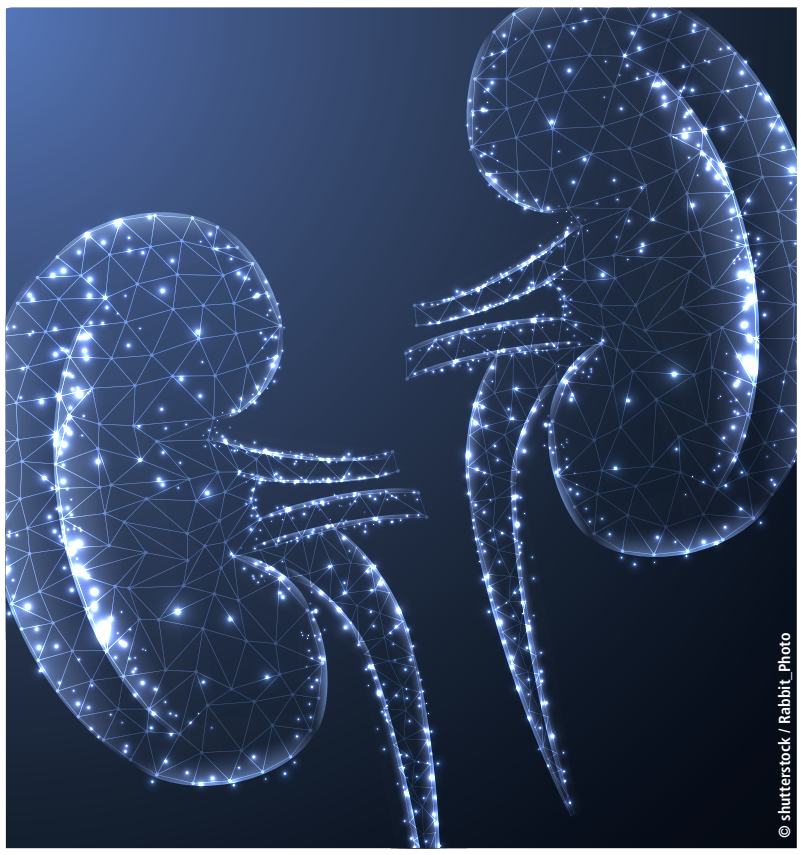
www.healthcare-in-europe.com

CONTENTS

Going digital

New frontiers for nephrology

Digital technology solutions are creating new opportunities for pathologists in diagnosis and assessment of renal conditions.



Digital solutions are creating new opportunities in nephrology

With the opportunity for whole slide imaging (WSI), improved workflow and better visualization, hospitals and laboratories are already seeing a return on the investment in such technology.

Artificial intelligence is also offering a new dimension and forging new frontiers in nephrology and, whilst it may still have limitations, clinicians are starting to understand and recognise the potential AI offers.

Advantages and hurdles

The challenges laboratories and hospital systems face in adopting digital solutions for nephrology were outlined during the 'Nephrology; New frontiers – nephrology goes digital' session during the online 33rd European Congress of Pathology. Delegates also heard about advantages and benefits detailed by five expert speakers.

Dr Pablo Cannata from the Hospital Universitario Fundación Jiménez Díaz (FJD) in Madrid, Spain, described advantages and hurdles of going digital, reflecting on the experience of the FJD pathology department, which introduced digital pathology in 2018 for renal pathology and uropathology. Within a year, almost all slides – except for cytopathology – were scanned digitally, though he acknowledged that some pathologists were initially reluctant to use digital pathology as the only solution for diagnosis. 'Some were still using microscopes,' he explained. 'But, by 2020, all our pathologists were using digital pathology as their most important diagnostic tool.'

Workflow improvements

Cannata explained that the main university hospital works as a reference hospital for three other hospitals from the group, with all the slides from the various scanners uploaded to the same cloud.

Other hurdles in the transition to digital pathology, he said, were the high initial cost, revision of the pre-analytical phase, and integration with the Laboratory Information System (LIS).

However, he said, 'There have been clear and wide-ranging advantages from going digital. These are the ability to offer telepathology in small pathology labs where there is no renal pathologist, it has delivered improvements in workflow, and supported annotation and quantification of pathologic findings.'

It also allows better and faster visualisation of serial sections, enables a global vision at different levels for more accurate diagnosis, and 'opens the door for computational pathology.'

Global application

Dr Vijaya B Kolachalama, Assistant Professor in the Department of Medicine at Boston University School of Medicine and the Department of Computer Science at Boston University, highlighted various aspects related to the role of AI in pathology. Machine learning, he said, can perform various tasks, such as diagnosis and staging of disease, biomedical segmentation, prognosis, and biomarker development (omics and drug discovery).

However, Kolachalama added, there are limitations to its global application, which depend on the location. 'For developed countries, or places with good clinical resources, the argument is that AI can assist the pathologist. For developing countries, or for places with limited clinical resources, the argument is that AI can serve as a tool to perform diagnosis/screening of patients. The sobering reality is that none of these tools are fully deployed in clinical settings. Tools are still largely under development.'

The reality gap

The 'exciting aspect': the field is open for researchers and entrepreneurs to build these technologies, and there is huge potential for telepathology.

Kolachalama said more publicly available kidney pathology datasets are needed that are representative of clinical practices globally to accelerate research in computational pathology.

He also underlined the importance of validation of computational algorithms to ensure that models developed on a single cohort of data are generalisable across other populations.

There also remains a gap between reality and hype surrounding explainable AI, and questions remain over demonstrating clinical and workflow benefits and who is going to pay for these AI-driven systems.

The session also covered having a Central Repository for Digital Pathology, which was discussed in a presentation by Renate Kain from the Department of Pathology at the Medical University of Vienna;

Dr Peter Boor, from the Pathology and Nephrology Department at RWTH Aachen in Germany, looked at pathomics as a novel tool for mining histology data; and Dr Romain Bulow, from the same unit, looked at deep learning-based classification of kidney allograft pathology. (MN)

Continued from page 1

Biosafety measures

There was also a lower number of patients being included in clinical trials and Hofman highlighted challenges and issues surrounding the use for translational research of human samples obtained during the Covid-19 pandemic from lung cancer patients.

Issues of biosafety measures and biospecimen handling resulted in a, decrease of specimens for diagnosis, and fewer collected samples also disrupted translational and basic non-Covid-19 research. A shortage of personnel also impaired routine work and research.

However, on the plus side there was a contribution to research on Covid-19 pathogenesis/pathology and a better understanding of the disease. In addition, the biological safety for personnel working in the pathology lab during Covid-19 had to be carefully assessed and managed with correct training and protocols.

The role of pathologists

Lung pathologists were particularly able to observe the changes taking place in the lung over the pandemic waves.

Professor Fiorella Calabrese, from the Department of Cardiothoracic and Vascular Sciences and Public Health (University of Padova, Italy), spoke of current knowledge of pathological lung lesions of Covid-19 and how to recognise and describe the major pathological lung differences through pandemic waves.

Pathologists, she said, had made an important contribution in this respect and had shown that from the first wave, there were three main phenotypes: with prevalent Alveolar Injury (AI); with prevalent Vascular Injury (VI); and with both (mixed type).

The second wave

During this, the most significant difference was a higher frequency of fungal infection, and in particular aspergillus, Calabrese explained. 'In terms of the important contribution of pathology, and the impact on clinical management, it had delivered clear-cut evidence of different injuries: e. g. vascular lesions. This has increased awareness about some therapeutic strategies (thromboprophylaxis).'

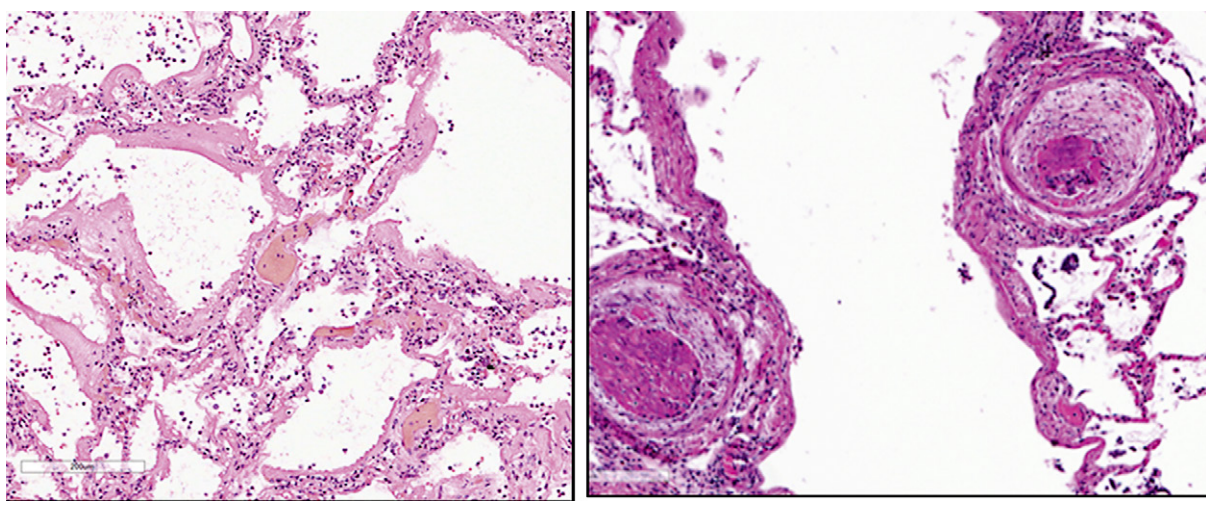
There had been identification of different pathological phenotypes in patients with severe disease and this led to the development of mathematic algorithms to predict different phenotypes.

There were also extensive tissue analyses from full autopsies, which increased a broader understanding of causes of death, because not all patients died due to severe Covid-19 pneumonia. 'With more superimposed infections – particularly fungal infections (CAPA) – this helped to enable the development of a diagnostic procedure for a more sensitive detection of proven CAPA,' she added.

The session also heard from Professor Zsuzsanna Varga (University Hospital Zurich), who discussed viral detection in the lung specimens, and Professor Ines Testoni from the University of Padova, who discussed how pathologists had reacted to the pandemic.

Professor Paul Hofman from the Laboratory of Clinical and Experimental Pathology at the Louis Pasteur Hospital in Nice, France, is Full Professor, Head of Human Biobank Unit at the University of Nice and of the FHU OncoAge. He obtained an MD at the University of Nice Sophia Antipolis and a PhD at the University of Montpellier and has published more than 500 articles in peer-reviewed journals.

Professor Fiorella Calabrese is a Full Professor in the Department of Cardiothoracic and Vascular Sciences at the University of Padova, Pathology Section. Her research includes pulmonary pathologies, transplant pathologies, molecular pathology, infectious and immunological diseases, and cardiomyopathies. She has authored 280 publications in peer-reviewed journals and is past chair of the European Society of Pathology (ESP) Pulmonary Pathology Working Group.

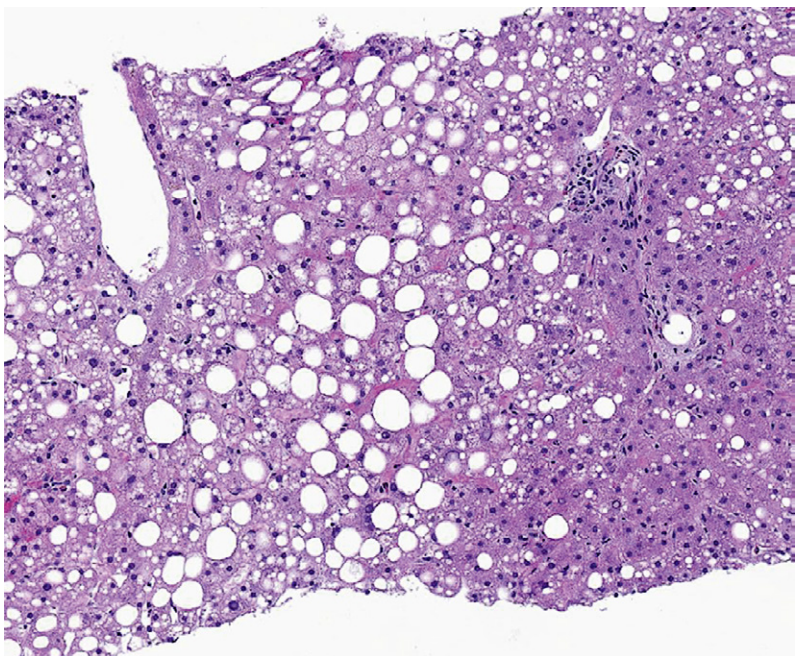


Left: Covid-19 pneumonia: acute lung injury. Right: Covid-19 pneumonia: vascular injury – microthrombosis

An estimated 800,000 deaths in 2030

Predicted: a liver disease pandemic

Based on recent studies of liver diseases, Professor Dina Tiniakos, pathologist at the National and Kapodistrian University of Athens, concludes that cases will soar worldwide by 2030, with 800,000 liver deaths related to NASH (Non-alcohol related steatohepatitis), costing health economies multi-billions of dollars.



Needle liver biopsy with severe steatosis. The vast majority of hepatocytes are filled with white lipid droplets. Haematoxylin & eosin stain x100 mag

Report: Mark Nicholls

During her presentation 'From the origins of NASH to the future of metabolic fatty liver disease' Dina Tiniakos outlined concerns in the keynote Symeonidis Lecture to the 33rd European Congress of Pathology.

The professor explained how NAFLD (Non-alcoholic fatty liver disease) – which includes NASH – is a complex metabolic liver disease with increasing prevalence.

Common causes

Abdominal obesity and type 2 diabetes are among common causes of a condition, which is now also referred to under a new definition of MAFLD (metabolic, dysfunction-associated fatty liver disease) to also include evidence of hepatic steatosis. In lean patients, that includes at least two metabolic risk abnormalities, such as prediabetes, insulin resistance, hypertension and increased triglycerides.

From simple NAFLD, some patients will progress to steatohepatitis (NASH) with liver inflammation and hepatocyte injury, of which 40% may show progressive fibrosis, and 3-5% of NAFLD patients may progress to cirrhosis. Detailing the history of the condition, Tiniakos said NAFLD has been overlooked for a long time – the term NASH did not exist in medical vocabulary until the 1980s. 'The fact that NAFLD has been overlooked for decades may be the reason that currently there is a lack of NASH-specific drugs and reliable biomarkers,' she added.

Liver biopsy

Fatty liver disease was first recognised in the 19th century, and became better identified due to liver biopsy used from the late '50s. Further recognition and understanding of NAFLD pathogenesis developed in the last three decades. 'Today,' Tiniakos continued, 'liver biopsy is still the most accurate method for diagnosing NASH and classifying NAFLD, but the natural history of NAFLD is dynamic and the disease may wax and wane, depending on diet, exercise and other factors.

'As disease progresses, fibrosis develops, and 20% of patients may be rapid progressors and may develop advanced fibrosis faster. It is important to identify rapid progressors to ensure they have the right management.'

Non-invasive diagnosis

There are, however, steps towards non-invasive diagnosis of NASH and fibrosis in NAFLD, including serum biomarkers, imaging methods to assess liver fibrosis and sequential combination of imaging with scores.

In primary care, non-invasive methods are useful, Tiniakos pointed out, to select patients at low risk of advanced fibrosis and while they can predict long-term outcomes and reduce need for liver biopsy – from 33 to 19 per cent – they cannot substitute the need for biopsy.

The professor warned that the future of metabolic liver disease looks worrying and global health systems should prepare for a NASH epidemic. This follows a 'call for action' by global experts to 'prepare for the NASH epidemic'.

NASH prevalence is in 1.5-6.5% of the population, but this is expected to increase to 63% by 2030. Up to 21 million Americans and 100 million individuals worldwide have NASH.

Future developments

NASH-related advanced fibrosis patients are likely to double by 2030; there will be 800,000 NASH-related liver deaths by 2030 and $95.4 billion will be the direct cost of NASH in the USA in the next two decades.

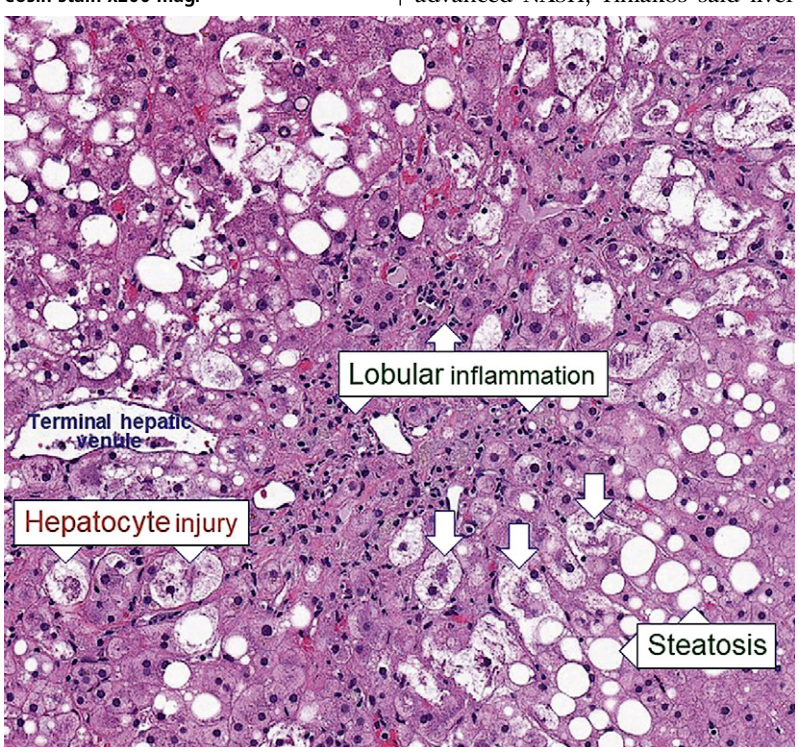
Whilst there are currently no approved drugs for treating NASH, more than 200 clinical trials are in progress.

Tiniakos also believes that pathological grading and staging of NAFLD/NASH in clinical trial settings in the near future may be supported by artificial intelligence methods.

She also pointed to advances in microscopy techniques such as second-generation harmonic generation/two photon excitation fluorescence imaging (SHG/TPE), and stain-free microscopy methods may improve reproducibility and standardisation of liver biopsy assessment.

In indicating that the future focus must be on establishing preventive methods, discovering accurate non-invasive diagnostic and prognostic biomarkers, and developing effective treatment for individuals with advanced NASH, Tiniakos said liver pathologists will continue to play a central role in this effort.

The minimal criteria for the diagnosis of steatohepatitis are steatosis, lobular inflammation and hepatocellular ballooning with a zone three (centrilobular) pattern of injury. Haematoxylin & eosin stain x200 mag.



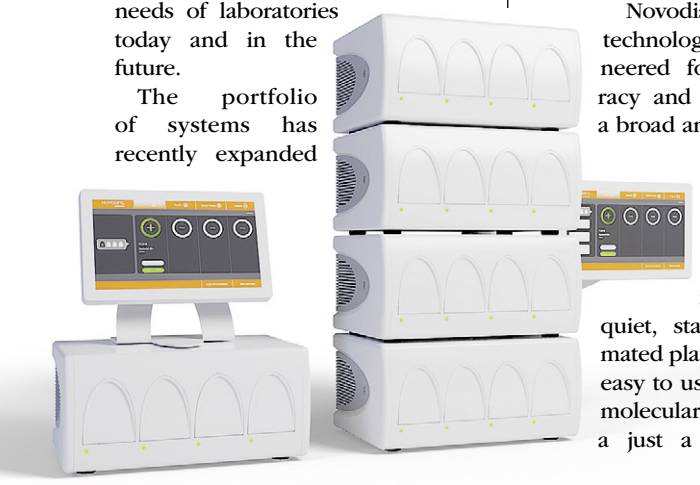
Professor Dina Tiniakos works in the Department of Pathology at Aretaieion Hospital, the National and Kapodistrian University of Athens, Greece, and the Translational and Clinical Research Institute in the Faculty of Medical Sciences at Newcastle University, UK. She is also Past President of the European Society of Pathology.

Meeting the needs of laboratories of every size

Molecular scaleable solutions

One size does not fit all when it comes to diagnostics. Different diagnostic locations need solutions that meet their needs, whether for on-demand testing in a healthcare setting or a laboratory managing population screening. Finding the right solution can be a challenge especially when the future may change what a laboratory needs, Hologic Inc. reports.

Hologic Molecular Scalable Solutions are well placed to meet the growing diagnostics testing needs of laboratories of all shapes and sizes, from a single patient rapid result in about an hour to population level screening, meeting the molecular diagnostic needs of laboratories today and in the future.



The portfolio of systems has recently expanded with the addition of the on-demand, molecular-testing Novodiag® system, Hologic's Molecular Scalable Solutions portfolio. This system offers a simple fast way to pinpoint patients most at risk with targeted, multiplex and syndromic on-demand testing.

Novodiag's high multiplex technology is precision engineered for simplicity, accuracy and affordability across a broad and growing menu of high- and lowplex assays to detect infectious diseases and for antibiotic resistance management. It is a small, quiet, stackable, fully automated platform that combines easy to use functionality with molecular performance. With a just a few simple steps the Novodiag system enables fast, life-saving diagnoses, delivering precise, easy-to-read results in an hour, so improving efficiency and bringing clinical confidence closer to the patient. Infectious diseases are detected from a single use cartridge in about one hour and a comprehensive menu of assays for screening of antibiotic resistances, gastrointestinal, respiratory (including Covid-19) hospital acquired infections is available. Each Novodiag assay can detect multiple targets simultaneously, for example, the Novodiag Bacterial GE+ assay has 14 targets, while the Novodiag Stool Parasites assay detects 26.

For settings that need a larger on-demand capacity, Novodiag PLUS links up to four instruments. These can be stacked and controlled by a single computer and offer a total of four independent slots per instrument, adding flexibility and convenience.

For laboratories requiring systems with a higher throughput, Hologic's Panther Scalable Solutions offer a range of options with a broad menu of high performing assays, allowing laboratories to expand their testing menu while adding on flexibility, capacity and walkaway time.

The portfolio's foundation is the Panther system, which was launched in Europe in 2010. This offers random access and full automation for molecular testing with a broad assay menu including tests for women's health, sexually transmitted infections (STIs), respiratory health, and viral load, as well as Open Access functionality for laboratory developed tests (LDTs). This menu enables laboratories to consolidate molecular testing onto a single platform.

The Panther system has additional add-ons including Panther Fusion, which launched in 2016 and provides additional IVD menu and the Open Access functionality, the Panther Plus, Panther Link and Panther Trax*.

The Panther Fusion module adds the ability to run real-time PCR, TMA and RT-TMA assays on a single, fully automated platform. This enables laboratories to consolidate testing, increase walkaway time and enhance flexibility.

With Panther Plus, laboratories can load more consumables directly on the instrument, allowing even greater walkaway time (up to 13.5 consecutive hours). Both fluids and waste can be changed while tests are in process, and an option for automatic liquid waste disposal is available. These features allow an additional 210 tests to be run in 24 hours, providing a total throughput of greater than 1,200 patient samples in that time.

Laboratories can gain additional efficiencies by using Panther Link, a software solution that creates a virtual connection allowing multiple Panther instruments to communicate with one another and function within a singular, streamlined workflow. Linked instruments can share information such as reagent kits and reflex test orders, enabling more efficient reagent utilisation and improved turn-around time. A dashboard command feature allows technicians to monitor instrument inventories, maintenance tasks and test results on a single screen from a centralised location.

Finally, the upcoming Panther Trax* will offer the ultimate in lab automation by physically and electronically linking multiple Panther instruments together into a single, powerful workcell that allows labs to increase testing volumes without increasing staff.

Taken together, these configurable options address the needs of today's laboratories, allowing them to increase operational capacity and testing volumes at their own pace, while building on the flexibility and streamlined user experience they require.

To find out more about how Hologic's Molecular Scalable Solutions can meet the growing pressure and demands of today and tomorrow visit https://www.hologic.com/hologic-products/diagnostic-solutions.

*Not CE-IVD, not for sale.
www.hologic.com

Body-on-a-chip technology

A boost for drug development

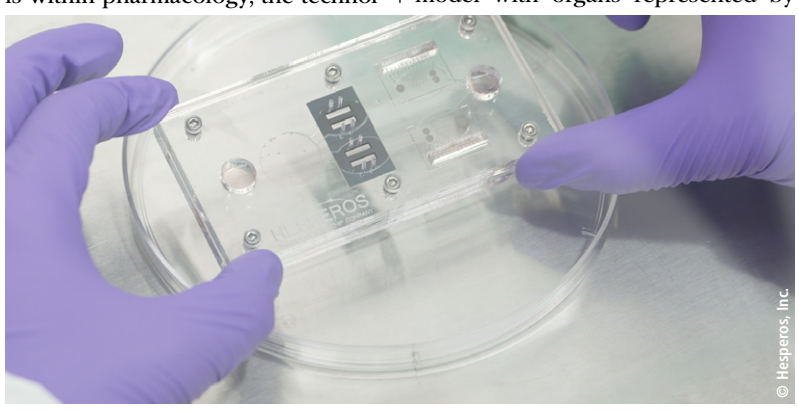
Integrating laboratory functions on a microchip circuit is helping to improve the cost-effectiveness of drug development.

So-called 'lab-on-a-chip' or 'human-on-a-chip' technology can highlight which treatments may, or may not, work before advancing along the clinical trial process. It can also have benefits for chronic and rare diseases, as well as helping shape personalised medicine.

Professor Michael Shuler, who is one of the pioneers of this technology, outlined how it has evolved. Over the past two decades his group at Cornell University in New York has applied chemical reaction engineering principles to biological systems to develop conceptual tools to test hypotheses about cellular mechanisms. This work combines mathematical models of subcellular and cellular mechanisms with models of the whole body as a means to relate the rapidly increasing insight from molecular toxicology and pharmacology with human and animal physiology via body-on-a-chip devices constructed on a microscale using the techniques of nanotechnology. 'My work has focused primarily on micro-physiological systems, or body-on-a-chip, where we try to emulate what happens in the body and use it in terms of drug development to determine which drugs may most likely be successful in clinical trials,' said Professor Shuler, who is Professor of Engineering Emeritus at Cornell and CEO & president of Hesperos, Inc. in Orlando, Florida. The technology integrates multiple analytic steps (such as measuring the time-dependent concentrations of drug and metabolites as well as cellular activities) on a single chip with the physiological-based pharmacokinetic models mimicking the integrated responses of organs such as the liver, colon, heart or lung to predict outcomes and reactions of proposed new therapeutical approaches.

Weeding out the drug candidates

The body-on-a-chip technology can also be used for rapid analysis or screening, and while Professor Shuler believes the main application is within pharmacology, the technology can be applied to toxicology and even to determine the safety of cosmetics. Professor Shuler said: 'At present, it is generally associated with pharmaceuticals and developing new drugs in clinical trials. A key question is how to decide which drug is best to take into clinical trials. About 10% of drugs in clinical trials are approved as useful. The rest are not, but it still costs a lot of money to go into clinical trials, particularly with those candidates that get to Phase III trials. So, if you could have a device which tells you which drugs in the human body are likely to fail and which are likely to succeed, there could be savings of hundreds of millions of dollars.



'The idea is to divide the body into different organ compartments and use the physiologically based pharmacokinetic model, in conjunction with a physical microscale model with organs represented by living cell constructs, to predict the efficacy of a drug (i.e.: 'does it work on a critical organ?') and determine the potential side effects. A whole-body model is needed because many drugs fail due to side effects even if they work on the primary target. The ultimate idea would be to have a system to improve the success rate of drugs in clinical trials.'

He said it is a fast-evolving field with major opportunities to improve the success rate for pharmaceutical companies in clinical trials. Professor Shuler, who was the first to demonstrate the feasibility of such body-on-a-chip systems, explained that while he focussed on the whole body on a chip looking at multiple organ systems and their behaviour, others have developed more specific systems for a single organ-on-a-chip, such as a detailed liver model for liver response, for example. 'Our model is a physiological model which predicts what will happen in the human, and is being applied to different diseases – some chronic and rare diseases, although cancer is a big area of application,' he added.

Finding the right diseases and target groups

With drug development, the technology can examine complications from drugs and how they may be affected by other medications patients are taking, before they are advanced to the clinical trial stage. 'It may be helpful for some chronic diseases where it could take the cells from a body and expand or use them directly to test multiple potential treatments and see which of those treatments work best,' he continued.

While a drug may work well in the majority of the population, there may be a proportion of the population in which they do not, so a clinical trial can be designed to select a subpopulation in which the drug should be tested. 'You can also build a system where you have representation of different types of phenotypes, people from different backgrounds and groups and see how the treatments will work,' he added.

Future applications

Professor Shuler suggests an additional area where the technology may be applied is the support of regulatory approval. In the future, he believes a strong application for the technology will be in personalised medicine, rare diseases, and immunological disorders where there are no robust animal models at present. 'Having a human-based model is better for predictions than animal models. In some cases, for example for rare disease where there are no animal models, it becomes essential,' said Professor Shuler. 'This kind of technology will have a major, or more immediate, impact because there is not a good alternative." (MN)

Michael Shuler is Professor of Engineering Emeritus at Cornell University in New York, having been the Samuel B. Eckert Professor of Chemical Engineering at the Meinig School of Biomedical Engineering. He maintains a funded research program at Cornell, which focuses on applying chemical reaction engineering principles to biological systems.

FREE Download Now!

Blackmagicdesign

Introducing DaVinci Resolve 17

Edit and color correct video with the same software used by Hollywood, for free!

DaVinci Resolve is Hollywood's most popular software! Now it's easy to create feature film quality videos by using professional color correction, editing, audio and visual effects. Because DaVinci Resolve is free, you're not locked into a cloud license so you won't lose your work if you stop paying a monthly fee. There's no monthly fee, no embedded ads and no user tracking.

Editing, Color, Audio and Effects!

DaVinci Resolve is the world's only solution that combines editing, color correction, visual effects, motion graphics and audio post production all in one software tool! You can work faster because you don't have to learn multiple apps or switch software for different tasks. For example, just click the color page for color, or the edit page for editing! It's so incredibly fast!

Professional Editing

DaVinci Resolve is perfect for editing sales or training videos! The familiar track layout makes it easy to learn, while being powerful enough for professional editors. You also get a library full of hundreds of titles, transitions and effects that you can add and animate! Plus, DaVinci Resolve is used on high end work, so you are learning advanced skills used in TV and film.

Creative Color Correction

DaVinci Resolve's color page is Hollywood's most advanced color corrector and has been used on more feature films and television shows than any other system! It has exciting new features to make it easier to get amazing results, even while learning the more advanced color correction tools. There's PowerWindows™, qualifiers, tracking, advanced HDR grading tools and more!

Designed to Grow With You

DaVinci Resolve is designed for collaboration so as you work on larger jobs you can add users and all work on the same projects, at the same time. You can also expand DaVinci Resolve by adding a range of color control panels that let you create unique looks that are impossible with a mouse and keyboard. There's also edit keyboards and Fairlight audio consoles for sound studios!

DaVinci Resolve 17 ..... **Free**

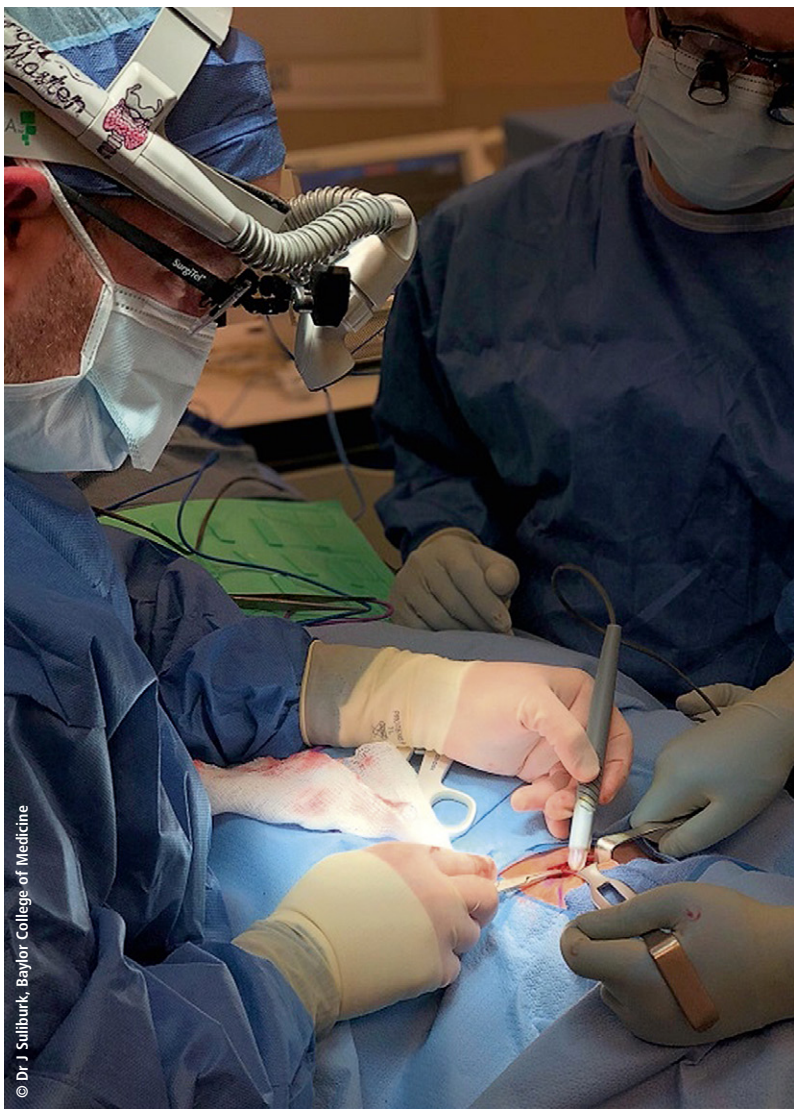
Optional Accessory
DaVinci Resolve Speed Editor ..... **255€***

Learn more at www.blackmagicdesign.com/nl

*Recommended retail price excludes VAT and shipping and delivery costs.

Pinning down the fringes of can

NEW: The MasSpec pen



Dr James Suliburk, head of endocrine surgery at Baylor College of Medicine, using the MasSpec Pen during thyroid surgery.

Mass spectrometry – a powerful tool for analysing the molecular composition of a tissue sample – is invaluable during cancer surgery. However, mass spectrometers are complex and unwieldy, and certainly a poor fit for an operating room (OR). To create a bridge between the lab and OR, Professor Livia S Eberlin, from Baylor College of Medicine, has developed a very promising 'pen'.

Report: Wolfgang Behrends

Surgical removal of cancerous tissue is a formidable tightrope walk: remove too little and a tumour could return; cut out too much and damage to the surrounding tissue becomes an issue – especially in vital organs. Where to draw the line when the border between cancer and healthy tissue is invisible to the naked eye? Mass spectrometry is the answer. 'Mass spec is an amazing tool to quickly measure and analyse molecules in a sample,' surgeon Livia Eberlin explains. 'The molecular makeup is highly reflective of our biological system – when we become diseased, its composition will change in a characteristic way, which can then be detected via mass spectrometry.'

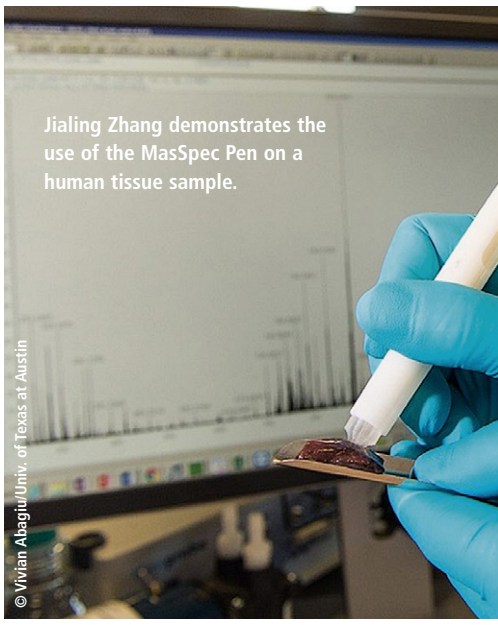
Put simply: when applied to a tissue sample, mass spectrometry can tell the difference between cancerous and non-cancerous cells. However, due to its complexity, the technology has largely been used in research and development laboratories, but has seen limited use in hospitals and operating rooms. The MasSpec Pen, a new tool developed by Eberlin's team, aims to change this. 'We envisioned and designed the MasSpec Pen to be an easy-to-use, handheld interface between the surgeon and the mass spectrometer.'

How it works

During surgery, the pen-size device is held against the tissue in question. 'The tip of the pen holds a droplet of water, which acts as a solvent to extract molecules from a sample. After three to five seconds of direct contact with the tissue, a vacuum transports the droplet to the mass spectrometer, where the molecules in the droplet are read.'

Using machine learning technology, the device has been trained to identify molecular patterns of different cancers, such as breast, ovarian, pancreatic or thyroid cancer. The system can translate this complex information into easy-to-read visual or auditory cues, Eberlin says. 'This might be a low pitch signal for healthy tissue, and high pitch for cancer, so that the surgeon could act upon this feedback immediately, while remaining focused on the patient.' To ensure hygiene and prevent infections, the contact areas of the pen are disposable but can also be sterilised with an autoclave for re-use.

While the information gathered from the molecular readout is not quite as specific as, for example, genetic analysis, the expression of the molecules offers a robust disease indication with accuracies ranging from 92 to 99 percent, depending on the cancer type. 'Still,' Eberlin warns, 'we need to be aware



Early detection – new diagnostic possibilities with MS qPCR

Newborn screening

Since its introduction around 60 years ago, the screening of newborns for immune, hormone and metabolic disorders has prevented many children from experiencing severe disease progression. The scope of systematic early testing has been significantly enhanced through mass spectrometry (MS). In our interview, Professor Uta Ceglarek, one of the driving forces behind the introduction of MS procedures in newborn screening, outlines new diagnostic possibilities offered by MS and qPCR procedures for screening – and also the ethical limits and possible dangers of new regulations for their implementation.

Report: Daniela Zimmermann

The foundations for using drops of blood from newborn babies to make predictions about the development and prevention of diseases later in life were laid in the 1960s with the systematic screening of babies for phenylketonuria (PKU). Professor Ceglarek deems this a success story, confirming, 'It has allowed us to diagnose diseases before symptoms develop.'

The expert views the inherited metabolic disorder PKU as a prime example of the importance of screening: Those affected lack an important enzyme which results in the amino acid phenylalanine not being converted into tyrosine. When phenylalanine is ingested through food it accumulates in the body – with serious consequences. 'Once these diseases take hold, the damage they cause is often irreversible.'

Due to the lack of tyrosine, untreated PKU can lead to severe impact on brain development, with resulting intellectual disabilities. Prior to the introduction of newborn screening, those affected required lifelong care and, in the most severe cases, had to be looked after in specialist care facilities. However, when PKU is detected early, the disorder can be managed well, with strict dietary measures, and specifically through the reduction of protein in the diet. 'The first patients who had PKU diagnosed during newborn screening are now aged over 40 and, due to early detection of the disease, lead normal lives,' Ceglarek points out.

MS/MS covers the lion's share

The range of diseases diagnosed through screening has increased significantly through the use of mass-spectrometry, and specifically through the tandem procedure MS/MS. The so-called enhanced newborn screening (funded by the statutory health insurers in Germany since 2005), currently includes 19 inherited diseases, nine of which are diagnosed via MS/MS [source: https://www.screening-dgns.de/richtlinien.php]. Additionally, PCR diagnosis, a procedure which has become more widely known to the public during the Corona pandemic, is used to diagnose severe combined immunodeficiency and spinal muscular atrophy.

The prerequisite for screening inclusion is the existence of a reliable diagnostic procedure and the respective disorder being treatable. Although curative care is not possible in all cases, such as in the case of mucoviscidosis, early detection helps to delay the progression of the disease and to increase the quality of life for those affected.

3-mm blood spot test for newborn screening

In some cases, the therapeutic opportunities improve over the course of time, meaning that screening of newborns still makes sense. Currently, this includes spinal muscular atrophy (SMA), which can be safely diagnosed via PCR, but which cannot be cured. Zolgensma (AVXS-101), a new medication introduced only this year, has brought a cure for muscular atrophy within tangible reach. 'Newborn screening for SMA started on 1 October 2021,' Ceglarek reports. 'The screening community is now observing with great interest how successful pre-symptomatic gene therapy will be.'

New legislation threatens diagnostic options

The new version of the EU In Vitro Diagnostic Medical Devices Regulation (IVDR), which will finally come into force in 2022, will make the use of new, but also of already established, self-developed procedures much more difficult, Ceglarek says.

This also affects mass spectrometry. On the one hand, all procedures developed in the laboratory must be newly revalidated before they can be used on patients. 'This means large, additional overheads for all parameters which need to be reviewed,' Ceglarek points out. On the other hand, the regulation prescribes the use of CE marked, commercially available laboratory tests. Even self-developed 'in-house' solutions, so-called LDTs, can only be used when there is no equivalent product available in the market, and only if they can prove full CE conformity. 'The IVDR is not about economic efficiency, meaning that the use of a different procedure must always be justified with reasons other than cost efficiency. This means that in case of comparable analytical characteristics, the commercial method must always be used.

This also has devastating effects on molecular diagnostics, which, to a large part, works with self-developed reagents. 'In our laboratory we are currently having to evaluate which LDTs we can realistically still offer,' Ceglarek explains, adding: 'If adherence to the IVDR had been compulsory at the start of the Corona pandemic, the initial supply of Covid LDTs would have taken a lot longer, because each procedure would have needed extensive validation before being used on patients.'

The new regulation could therefore turn into a nail in the coffin for

ncer

of potential error, be it from mixed tissue composition in dispersed cancers or other tissue features, such as necrosis, which potentially could skew the analysis. But, overall, the powerful insight gained is clearly worth it.'

One of the main appeals of the device is its quick result delivery. This is a huge upgrade compared to the current standard, which is frozen section analysis of the tissue. 'When the sample needs to be taken out, sent to a pathologist and analysed, it takes a lot of time. Also, the freezing process can alter the sample tissue, which may affect diagnostic accuracy. The MasSpec Pen keeps the process within the OR and provides results within 15 seconds in vivo or from the freshly excised tissue. This circumvents the need to move and freeze the tissue.'

Potential for further applications

Currently the pen is being validated for patients in clinical studies at Baylor College of Medicine and the MD Anderson Cancer Center, both in Houston, Texas. According to Eberlin, the device can essentially be used in any type of solid tumour, which opens up many additional applications, such as prostate or brain cancer.

Additionally, the developers are exploring the potential of the pen in forensic settings, for example to detect illicit drugs on surfaces or pesticides in fruit. 'We even used it to determine certain kinds of meat and fish, which might be mislabelled as higher-quality products to achieve a higher price on the market,' Eberlin says.

However, to avoid taking on too many aspects at a time, current clinical studies focus on the pen's application in breast, pancreas and ovarian cancers. 'We are taking this one step at a time,' Eberlin says. 'Right now, we are probably three to five years from deployment in hospitals.' Besides fine-tuning the technology, a lot of this time will be taken up by regulatory steps, such as submitting the design to the U.S. Food and Drug Administration (FDA) for approval as a medical device.

Meanwhile, Eberlin is confident that the MasSpec Pen has the potential to be a great asset to surgeons in removing all cancer cells and thus will improve patient outcomes.

Livia Schiavinato Eberlin is an Associate Professor in the Department of Surgery at Baylor College of Medicine and Adjunct Professor in the Chemistry Department at the University of Texas in Austin. Her research group is focused on developing mass spectrometry technologies to address critical problems in health-related research.

Professor Uta Ceglarek is Deputy Director of the Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics (ILM) at the University Hospital Leipzig, where she has been heading the Newborn Screening Laboratory since 2005. After completing her chemistry degree and a doctorate in analytical chemistry, Ceglarek completed further training in toxicology and clinical chemistry. In 2010 she was awarded her professorship, writing her habilitation on clinical metabolome research. Since 2000 she has been working on the use of mass-spectrometry diagnostics in newborn screening, for therapeutic drug monitoring and for metabolic indications. Ceglarek is also president of the German Society for Newborn Screening (DGNS) and speaker of the Section for Clinical Mass Spectrometry at the German Society for Clinical Chemistry and Laboratory Medicine (DGKL).

many laboratory-diagnostic procedures, such as those for diagnosis of rare diseases. 'If the validation of these tests is this comprehensive, it will no longer be viable to offer them, so important diagnostic procedures will no longer be commercially available and cannot be offered as LDTs,' Ceglarek says, appealing to those in charge, and calling for the IVDR to be modified before the end of the transition period.

4,000+ laboratories worldwide h

Outlook: Lab automation

Innovations in technology continue to improve clinical laboratory productivity. Total lab automation systems are responding to dramatic growth in internet-driven streamlined processes.

Report: Bernard Banga

In 2021, around the world, microbiology labs in commercial and university teaching hospitals have been processing more files and data then ever and systems are constantly reorganising to reach a critical mass for profitability.

Objectives: to reduce the time needed for reports, speed up workflow and improve overall sensitivity of results.

This year, a dozen major operators have business units in this sector, including the world's top five in vitro diagnostics (IVD) companies: Roche Holdings, Thermo Fisher Scientific, Abbott Laboratories, Becton Dickinson Life Sciences and Siemens Healthineers.

Covid-19: Increased testing volumes is unprecedented

The world still grapples with the impact of the ongoing Covid-19 pandemic, which has intensified research as well as added pressure on pharma and clinical labs. Ensuring quicker turnarounds has become the priority, which leads to greater demand for automated liquid handling, microplate readers and robotic systems. Immunology and serology testing have gained importance during this pandemic, now in its third year. There has been significant deployment of polymerase chain reaction (PCR) and quantitative polymerase chain reaction (qPCR) techniques in laboratories and hospitals, to improve Covid-19 testing capacity.

This unprecedented increase in testing volumes presented a great opportunity to ramp up automation in immunology diagnostics, clinical chemistry and haematology labs.

© shutterstock / Sergey Ryzhov

Mass spectrometry and TLA

According to Professor Gian Luca Salvagno, in the department of clinical biochemistry at the University of Verona, Italy, 'The spread of laboratory automation is also embracing mass spectrometry.' The new generation of pre-analytics workstations, which can be connected directly to mass spectrometer systems, will allow the automation of manual extraction and the elimination of time-consuming activities, such as tube labelling, capping and de-capping.

'The use of automated liquid-handling platforms for pipetting samples and protein precipitation reduces turnaround time and increases throughput in mass spectrometry testing,' Salvagno added. The development and integration of different technologies into automated mass spectrometry (MS) analysers will also generate technical and practical advantages, such as pre-packaged, ready-to-use reagents, automated dispensing, incubation and measurement, automated sample processing, multiplex testing and automated validation and interpretation.

Total lab automation embeds in biochemistry labs

Today, total lab automation enters a new phase. Laboratories are investing heavily in Total Lab Automation (TLA) systems supplied by in vitro diagnostics companies. These systems combine to form an integrated system for total automation of pre-analytics, processing, clinical chemistry and post-analytics immunochemistry workstations. The aim is for specimens to be processed, analysed, and even stored with minimal user intervention. According to the American Association for Clinical Chemistry (AACC), 4,000+ laboratories worldwide have now installed automated systems.

Robotic systems or centralised hubs in Europe

On the one hand, mid-sized facilities (1.5 to 6 million tests annually)

Cyber attack: Be prepared!

Will your system beat ransomware?

Ransomware attacks are a highly profitable and flourishing business in the 21st century. They can have a drastic impact on hospitals, clinical laboratories, and patients, Cynthia E Keen reports.

The Sophos Group, a British security hard/software company, has reported survey responses from 328 healthcare IT managers in 30 countries. These reveal that 34% experienced a ransomware attack in 2020. Of these, about 40% could stop the attack before data was encrypted, but 34% paid unspecified ransoms to restore only 69% of their data. The average cost to attacked facilities was $1.27 million, representing downtime, staff/device/network costs, and ransom paid.

In a recent seminar, two experts in prevention and mitigation of ransomware attacks provided practical advice to clinical laboratories on how to prevent attacks and what to do if an attack occurs. Emily Johnson, a Chicago-based healthcare attorney specialising in data breach mitigation, discussed the components of a proactive ransomware data breach mitigation plan for clinical laboratories.

Based on a comprehensive, written information security program, it should include annual risk assessments, a detailed basic cyber incident response plan, a resiliency plan, and a plan for internal and external communications. Labs should have confidentiality agreements for employees and vendors and should conduct due diligence to confirm that people or companies they are doing business with also deploy breach prevention measures.

Prepare employees

Ongoing training is essential. In addition to enhancing awareness and knowledge about security risks and to reduce the risk of accidental human error, employees need to know how to identify, report, and respond to a possible security incident.

Labs should regularly perform data privacy reviews and penetration testing. Johnson recommends the use of internal phishing missions, sending emails to employees and any other individuals or vendors who have access to lab's operations that appear to be coming from a trusted sender, to identify who responds.

Paul Caron, senior director of incident response at Arete, a global cybersecurity consulting company, emphasised the importance of assessing emails to learn the volume of potential spam and phishing. 'Phishing allows an attacker to distribute a weaponised payload or spoofed website to many recipients. Credentials are compromised or trojans added to establish a foothold within the environment, allowing remote access into the environment and harvesting of legitimate credentials of employees.'

Be wary of remote desktops

Remote desktops available to the internet can pose major security concerns. 'Attackers will use brute force or compromised credentials to log into the specific system that is openly available externally. After gaining access to the system, the threat will compromise further credentials or begin to move laterally throughout the IT environment.'

Endpoint detection and response (EDR) technology can facilitate the process. EDR security systems use behavioural analysis to analyse the activity of unusual behaviour attributed to individual users. They monitor and collect activity from endpoints that could be a threat, analyse this data to identify threat patterns, automatically respond to identify threats to remove or contain them, and immediately notify security personnel.New guidance released by the U.S. Cybersecurity and Infrastructure Security Agency (CISA) emphasises the importance of maintaining offline, current, and encrypted backups of data and regularly testing them. When internet-facing vulnerabilities and misconfigurations are identified, they need to be immediately mitigated.

Recommendations in case of a cyberattack

When a hacking incident occurs, it is critical to identify what data has been exposed and to determine the scope of the attack. Caron recommends the following actions when a security incident is identified:

- Immediately retain digital forensics and incident response specialists, who have expertise on ransomware attacks and can expedite internal assessment.
- Leave all systems on; do not power down or reboot systems. Many ransomware variants do more damage or further encrypt systems upon reboot.
- Disconnect inbound and outbound network activity, network interface cards and internet LAN cables to prevent any connection to the Internet.
- Obtain snapshots or full disk images of critical systems and servers, and potential 'Patient Zero' systems to facilitate a forensic team.

If real-time backups exist, a lab needs to determine if the amount of time to restore via backup is acceptable.

If negotiations seem necessary to restore operations rapidly, a key element that labs need to consider is whether it would be appropriate to negotiate for specific hacked systems at a lower payment rate.

Caron suggests that demands from the hacker be carefully assessed, and that a plethora of data be acquired to aid in negotiations. He recommends

© shutterstock / supimol kumying

have installed automated systems

in 2021

are often equipped with only the latest generation compact systems combining clinical chemistry and immunoassay activities, taking up around 2 m², allowing a throughput rate for tests of 870/hour. 'Larger laboratories tend to invest in bigger systems, or even in several systems in parallel, integrating the haemostasis and haematology sections,' explained Marie Rolin, mission manager at Alcimed, a French consulting company focusing on innovation and development of new markets.

In Europe, university teaching hospitals constitute the main contingent of laboratories to have adopted robotics systems. Whereas university hospitals in Germany, the United Kingdom and France are generally equipped with a maximum of 2 TLA stations per facility, a specific feature is emerging in Italy and Spain where regional technical platforms are regrouping into gigantic centralised 'hubs', sometimes with up to six TLA stations in parallel.

Connecting challenges for digital transformation

All stages of analysis can ultimately be combined under TLA – provided, crucially, that the analysis instruments can work at the same speed as the tube conveyor. However, one issue looks big for full lab automation: equipment upgrades. For suppliers of diagnostic instruments, the opportunities associated with TLA innovation have been quickly overshadowed by the urgent need to upgrade. 'The choice of upgrade instruments for immunology, clinical chemistry, haemostasis and haematology is now frequently reliant on their compatibility with TLA systems,' Rolin pointed out.

Emerging AI-based tools for Total Lab Automation

The current need for automation is increasing largely owing to the dramatic growth in internet-based processes. Connecting devices to the internet enables remote patient monitoring, alerts, management, etc. Digital transformation is driving growth in this market. As manual systems still expose the process to the risk of error, implementing Internet of Things (IoT) systems helps to collect data both digitally and accurately, which has been shown to reduce the time needed by 60%.

IoT also offers IVDs the ability to interact directly with the support layer, allowing events to be captured electronically. As connected technology and cloud-based laboratory information management system (LIMS) platforms evolve, new tools emerge. These help companies to reap the rewards of digital transformation. The internet-based tools provide labs with a secure means for organising data, allowing quick and easy access to information, while allowing companies to exercise control over data sent to third-party instrument providers.

Finally, systems implementing IoT will be able to deliver server control and monitoring of various sensors, and can easily be configured to handle further hardware integration modules. Sensors fitted to devices can assist with data collection and communication with the cloud and other devices.

Attorney **Emily Johnson** specialises in healthcare industry issues at McDonald Hopkins, a business advisory and advocacy law firm in the USA. She has significant experience with HIPAA privacy act compliance and advising clients on proactive ransomware attack breach prevention.

Paul Caron is a Senior Director of incident response at Arete, a global cybersecurity consulting firm. He assists clients throughout digital forensics and incident response (DIFIR) engagements, most commonly in the form of complex ransomware attacks and business email compromise.

that only an initial partial payment be made to determine if the ransomware attack group can show proof they can restore the encrypted data. Some can destroy more effectively than they can restore. 'Ransomware attacks tend to occur at the end of a day, the end of a regular workweek, and on holidays. Always be vigilant.'

Early detection

AI technologies advancing cancer care

Cancer care and the treatment clinicians can offer patients is being increasingly enhanced by artificial intelligence.

Report: Mark Nicholls

AI technology has a role in diagnosis, with algorithms trained to design and deliver patient care. It can match patients to clinical trials they may benefit from, and even help to predict outcomes and people who are at greatest risk.

The session, 'New Frontiers of AI and Data Analytics in Oncology' at the online HIMSS21 European Health Conference explored where AI and data analytics is having the greatest impact today: screening and early detection, auto-planning for radiotherapy, treatment optimisation, identification of new biomarkers and more.

Innovative technologies

Clinicians are constantly seeking new ways of developing and implementing innovative technologies to support transformation of cancer care delivery, with AI pivotal to that, said Dr Tufia Haddad.

But while new drugs and treatments are being approved on a weekly basis, she emphasised that they are only relevant if oncologists and their teams are up-to-date with the advances to ensure the right drugs reach the right patients.

'With this in mind,' she said, 'we aim to develop clinical decision support tools for our oncologists to help them select the best care, whether it is a standard care treatment option, or a clinical trial opportunity.'

Her presentation 'Improving Patient Health and Provider Efficiency with Advanced Clinical Decision Support Systems' highlighted how the Mayo Clinic in the United States is working with commercial partners to develop a clinical trial matching system that extracts information from electronic health records to ensure patients match the trial's inclusion and exclusion criteria.

'We use natural language processing and machine learning to train the system to identify patient tumour attributes in order to match inclusion and exclusion criteria in individual clinical trials,' said Dr Haddad, who is an Associate Professor of Oncology at the Mayo Clinic College of Medicine and Science, and a Consultant in the Department of Oncology.

Sustained impact

Once brought into practice, there was an immediate and sustained impact in how the system allowed the providers to better understand the clinical trial opportunities.

'Because they were doing it more efficiently,' she continued, 'they had more time to spend counselling the patient about the potential benefits of participating in a clinical trial. We also saw a dramatic increase in our clinical trial accrual, both to our cancer-specific study as well as our broad Phase I experimental cancer therapeutics programme.'

Another priority is to develop a model to better assess breast cancer risk.

'I really believe that having AI-enabled advance clinical decision support systems can improve provider efficiency, engagement and effectiveness,' she said. 'For cancer risk assessment, it can help us individualise risk with increased accuracy and, overall, this has the potential to allow us to better tailor our screening and prevention recommendations to patients and reduce morbidity and the cost of care as well.'

Professor Matteo Pepa is a Biomedical Engineer in the Division of Radiation Oncology and at the Radiomic Group of the IEO European Institute of Oncology IRCCS in Milan, Italy. He is also adjunct professor at the University of Milan. His fields of expertise include medical imaging, artificial intelligence, radiomics and radiation oncology.

Professor Barbara Alicja Jereczek-Fossa is an Associate Professor of Radiation Oncology at the University of Milan and Head of the Department of Radiation Oncology at the IEO European Institute of Oncology IRCCS in Milan, Italy. Her main research and clinical interests include urological malignancies, breast cancer, combined modality approach, and high precision radiotherapy.

Dr Tufia Haddad is an Associate Professor of Oncology at the Mayo Clinic College of Medicine and Science, Chair of Digital Health for the Department of Oncology, and serves as the Mayo Clinic Cancer Center Associate Director for Practice Innovation Platform. Her clinical practice and research are dedicated to breast cancer.

Decision support tool

Professor Barbara Alicja Jereczek-Fossa, Associate Professor of Radiation Oncology at the University of Milan, Italy, and Head of the Radiotherapy Division at the European Institute of Oncology, Milan, outlined how radiation oncology has an essential role in cancer management, contributing to cure in about 40% of all cancer patients.

But with a huge amount of data to study to gain more knowledge on prognostic and predictive factors, AI is increasing in importance.

Her colleague, Professor Matteo Pepa, a bioengineer working on AI in Jereczek-Fossa's department, highlighted how AI plays a role in the radiotherapy workflow steps of patient consultation, planning, image acquisition, segmentation, radiotherapy delivery and follow-up. 'AI can be used as a decision support tool for radiation oncology,' Pepa said. 'The radiation oncologists can put their mind to the best course of treatment before expending resources on a lengthy treatment planning process.' With image acquisition, AI is utilised in synthetic image generation, CT artefacts reduction, and image quality improvement.

Deep learning can help determine optimal radiation parameters, Pepa said, and reduce planning time while improving the quality of images.

'The last step is radiotherapy follow-up and artificial intelligence and machine learning models have been proven to be successful in predicting outcome,' he added.

Radiology workflow

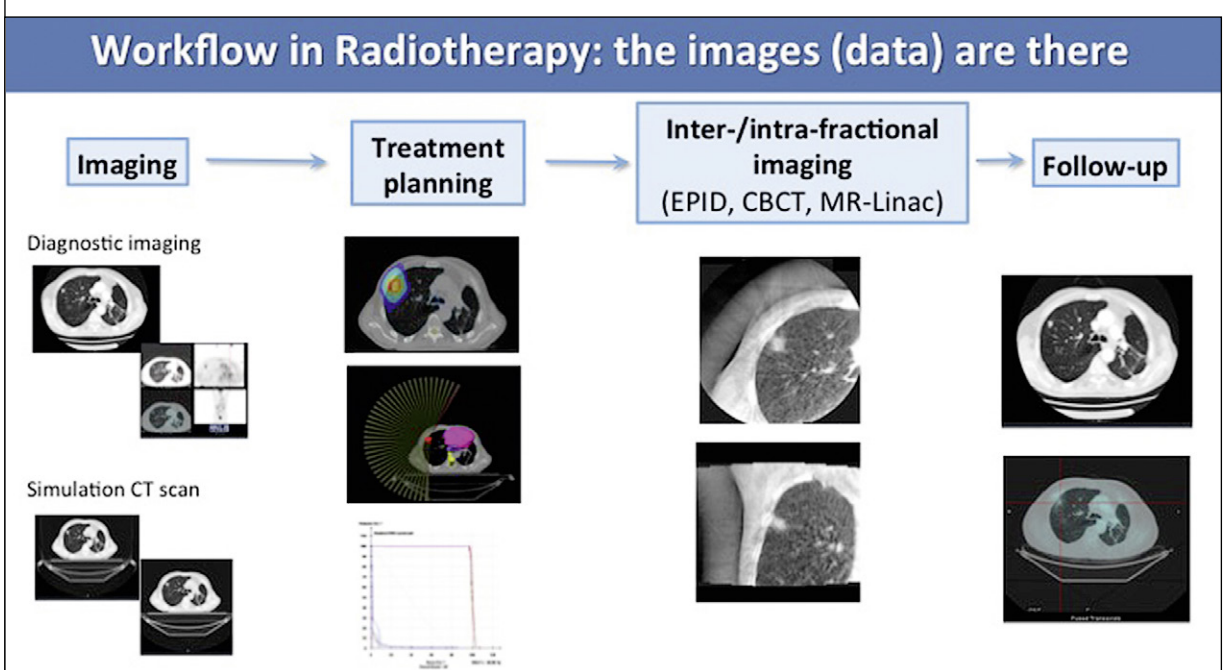
The session also heard from Mathias Goyen, GE Healthcare's Chief Medical Officer for Europe, who outlined examples of where artificial intelligence is streamlining radiology workflow, automating repetitive and tedious tasks to allow the radiologist time to focus on their core roles. He gave examples in breast and prostate cancer, where technology is offering support.

'One challenge for clinicians regarding breast cancer is how to increase detection rates, how to reduce false positives and how to avoid unnecessary patient recalls,' Goyen said.

He outlined how a GE Healthcare workflow solution used deep learning that allows for advanced cancer detection, a significant improvement in workflow and delivered reading time reduction of almost 30 percent.

Another example was an AI-powered advance visualisation review and reporting tool for prostate MRI.

'AI can be deployed to streamline workflows and support the radiologist in creating richer and more definitive reports, which can translate into more informed clinical decisions with a higher diagnostic confidence,' Profesor Goyen pointed out.



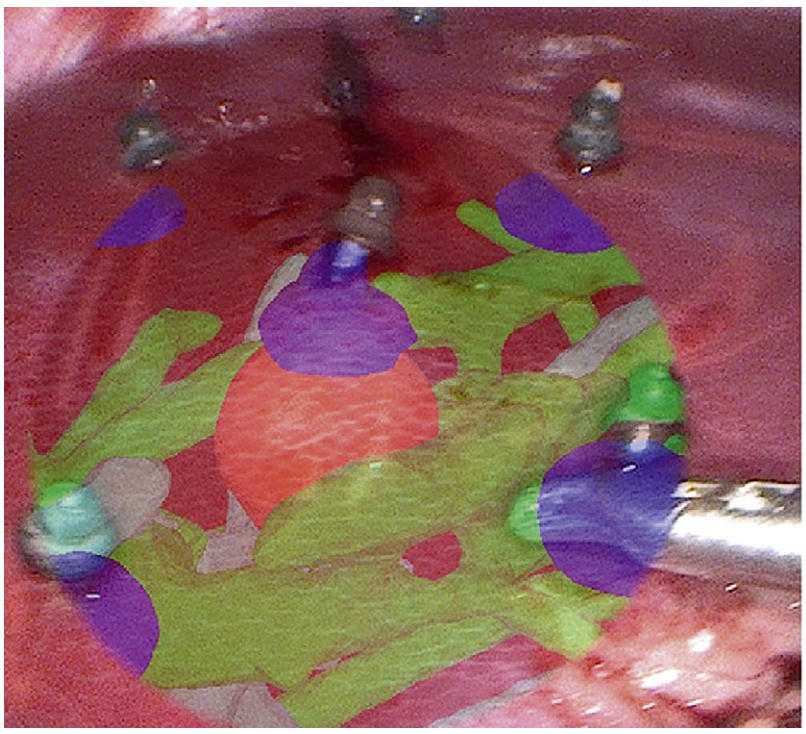
The whole workflow in radiotherapy is based on medical images, a potential source of information on tumour biology, on- and post-treatment tumour remission. AI will help to analyse these images and create decision support tools. CT: computed tomography; EPID: electronic portal imaging device; CBCT: cone beam computer tomography; MRI-linac - magnetic resonance imaging-based linear accelerator.

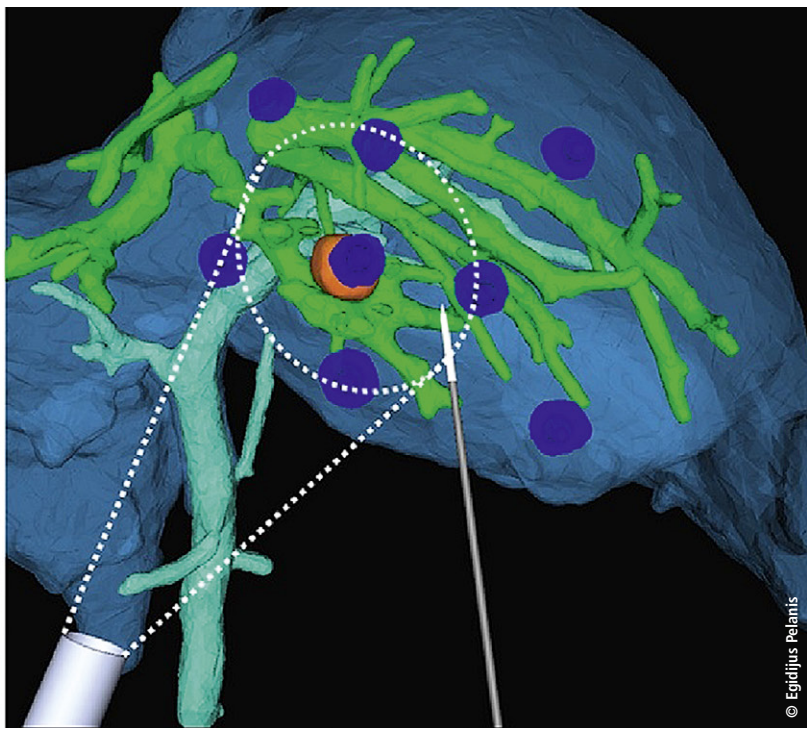
'XR is fusing surgical reality with medical images'

Extended realities in the operating room

Leading medical extended reality (XR) experts gathered at Shift Medical to discuss developments on the use of immersive technologies in medicine. For European Hospital, Sascha Keutel interviewed Doctor Egidijus Pelanis of Oslo University Hospital about applying extended realities in the operating room.

'Virtual reality (VR) is often used for education and training, for example in anatomy teaching, where the students can examine the virtual models,' Egidijus Pelanis explained. 'In medical school, the students train on artificially created anatomical models. If it is not a cadaver, or comes from patients' images, the models are standardised. But that's not how it is in reality because patients have anatomical variations. In VR, you can create highly detailed and realistic patient-specific 3D models. The users can also be placed in life-like environments, simulations, and use controllers to get haptic feedback during interactions to train before the actual procedure.'





Augmented reality laparoscopic image

Augmented reality (AR)

'AR comes closer to the actual surgery because virtual images can be overlaid on top of the real-world object. In the Intervention Centre at Oslo University Hospital, we have tested AR for laparoscopic liver surgery.

Here, the user can place 3D models and see these virtual elements in the 3D camera view. However, there are still some limitations related to the complex workflow, visualisation and how these virtual elements should be presented on the laparoscopic camera view.'

Mixed reality

'In Mixed Reality (MR), the user views the digital images in the physical world and interacts with them. At our hospital, we're working with Microsoft's HoloLens 2, which allows us to put virtual objects into our environment. We create holograms of patients to walk around and to look at their anatomy and pathology individually, or in groups of clinicians. 'It enables us to visualise and explore different treatment strategies in several disciplines – liver surgery, congenital heart surgery, orthopaedic surgery, and so on. 'One of the advantages of using MR is that the clinicians are more accessible and not bound by the physical location of the hardware. With a head-mounted mixed reality device, one can see a model with depth as if it were in real life and can point and interact using one's hands. You can toggle the visibility of the virtual elements or peek inside to better understand the spatial distribution of the anatomy and pathology.'

Challenges to XR implementation in surgery

'It's crucial to remember that patients are in three dimensions, but medical professionals still focus on flat images for decision-making. For education and case reporting, documentation is commonly limited to text or annotations on medical images. It is constrained and needs a lot of imagination to understand where all these locations are inside the patient. By creating 3D volume renderings and holograms, you can point and show virtual models and combine all these mediums and information for more detailed documentation.

'However, one major challenge is the preparation of XR, the data that needs to be processed into 3D models and holograms. Hospitals are sitting on a lot of unprocessed data they still use for the traditional way of examining. 'I believe that doctors, surgeons, and even patients should start asking for 3D representations of their anatomy and pathology.

'Then again, to create 3D models of every patient, you need to have sufficient evidence that it will help, that you cannot make the best decision for the patient without it. Hospitals are sitting on this resource, but too few are processing it; too few are bold enough to invest without solid evidence that having that data processed will be important in the future. But the proof can only be established if someone spends enough time on this and publishes the research results.'

Different navigation and visualisation methods in XR

'Medical images can be used, for example, to create virtual 3D models to lay over the patient during surgery. Once patient-specific 3D models are created, physical and virtual spaces can be combined with tracking technology. You can, for example, have an optical tracking system with cameras in the OR that detect spheres placed on various objects to be tracked. This enables real-time tracking of objects and the ability to place virtual elements in the OR. These fused scenes and images can be presented either on screens, in augmented reality, or in mixed reality.

'This process can need some navigation system set up and a certain amount of input from the users. HoloLens offers eye-gaze control so that some functions can be controlled by looking at them. For example, when the surgeon's hands are occupied during surgery, he can look at and activate certain buttons for interaction to reduce the physical clicking of buttons.'

Pelanis: A 'perfect' future Operating room

'Today, we miss a complete solution for integration. Existing and new technologies in the OR are mostly independent; they have different systems and standards. 'I see a bright future where all systems talk to each other, where images and information are synergistically flowing between devices; I see decision-support mechanisms using AI that provide automatic patient- and user-specific workflow in which next steps are predicted and shown. 'Maybe the patient lies on a table and complete patient data is shown holographically in the surroundings. Then treatment is performed by a robot-assisted surgical system with current and accurate visual controls that support surgeons in their intraoperative decision-making and surgery. 'Whatever new gadgets or technologies are brought into the OR, I hope these will seamlessly integrate into the whole imaging, diagnostic and treatment workflow.'

Could XR become the new standard for surgery?

'First, we should remain focused on the patient by improving patient care from a value-based healthcare perspective and not get distracted by all futuristic emerging technologies – which resonate with our Sci-Fi fantasies from childhood. 'Secondly, I think XR will stay. Various modalities will find their place in healthcare systems. Surgeons, and clinicians in general, will use what they have available and what works best. We are always looking for solutions to solve problems, to treat the patient. XR is one potential candidate for solving particular communication, visualisation and navigation challenges.

Randomised controlled trials needed

'At first, it might have been curiosity about the gadgets and cool holograms. However, research is starting to gather knowledge and examples where XR could improve certain aspects of care. Though we still need more research, e.g. randomised controlled trials that provide evidence that when doing an intervention in three dimensions on a patient, we will have to see and plan those in 3D using XR devices.

'In addition, the definition of XR could evolve as new devices and gadgets are developed. Also, there are unexplored territories with projections and beyond wearable devices; I imagine some AR with screenless and glass-free 3D coming to the OR in the near future.'

Egidijus Pelanis MD is a PhD candidate working at The Intervention Centre, Oslo University Hospital in Norway. He works with healthcare technologies and is part of both the Section of Clinical Research and the Section of Medical Cybernetics and Image Processing. Egidijus is researching the use of various navigation and visualisation methods for minimally invasive surgery.

Saving lives

Mobile stroke units

Speed in treatment of ischemic stroke can mean the difference between successful recovery versus permanent disability or death caused by brain tissue damage.

Report: Cynthia E. Keen

Time is of the essence to perform thrombolysis with a tissue plasminogen activate (tPA), a protein that can dissolve blood clots causing the stroke or intra-arterial thrombolytic therapy (IAT) because of large-vessel occlusion.

CT imaging to rule out intracranial haemorrhage is essential to determine if this treatment is appropriate. In 2003, Professor Klaus Fassbender MD, director of the Neurology Clinic at Saarland University Medical Center in Homburg, Germany, proposed the idea of expediting CT imaging by bringing a CT scanner to the stroke victim in a specially configured 'stroke ambulance'. His idea to shift acute stroke examination, including brain imaging, to a prehospital setting became reality with the 2008 launch of the world's first mobile stroke unit (MSU) at his hospital, which serves mixed urban and rural communities in a 20 km radius.

© UTHealth

The Houston Mobile Stroke Unit.

MSUs incorporate a compact CT scanner, a complex point-of-care laboratory equipped with small, commercially available portable laboratory devices to quantify haematological, clinical chemistry, coagulation markers, and renal function markers; real-time bidirectional audio-video communications, and a PACS workstation. Clinical staff onboard typically include a paramedic, CT technician, and physician plus a registered nurse trained in stroke medicine. A neuroradiologist should be accessible via PACS, and telemedicine connects with a hospital's laboratory staff, emergency physicians, neurologists, and/or neurosurgeons.

Blood clot-busting medication: Sooner in MSUs

MSUs shorten time to treatment, improve prehospital triage, and can increase thrombolysis rates. A study presented at the 2021 American Stroke Association's International Stroke Conference from Memorial Hermann Texas Medical Center in Houston reported that stroke patients treated in MSUs received blood clot-busting medication more frequently and sooner than patients who received initial care from emergency medical technicians in a standard ambulance. James C Grotta MD, director of the Houston Mobile Stroke Unity Consortium, called MSUs 'a stroke centre on wheels'. Grotta reported that 53% of patients treated on an MSU in his study made a complete recovery, compared to 43% who were not treated on an MSU. Memorial Hermann Health System is sponsoring an ongoing randomised interventional clinical trial, the BEST-MSU Study, which began in August 2014 with an estimated enrolment of 1,038 patients.

The completed study will provide data on outcomes and cost of MSUs compared to standard ambulances, and will help determine the value of integrating MSUs into hospital stroke programs in the USA.

'This study will provide critical information that will be needed to determine if and how a subsequent more definitive study should be conducted. It is a necessary first step in a process which may dramatically modify the way that acute stroke patients are managed in the United States,' Grotta pointed out.

Currently there are fewer than 30 MSU programs in operation in the USA. Major roadblocks to implementation include cost, staffing, and the ability to identify individuals who have had a stroke by emergency telephone call dispatchers.

Clinical trials performed in Europe

A number of clinical trials have been conducted in Europe, all of which produced data supporting the benefits of MSUs to stroke victims.

A randomised clinical trial performed in Homburg between 2008 and 2011 showed that MSU-based stroke management significantly reduced time to treatment from 153 minutes for ischemic stroke patients receiving standard care to 72 minutes with an MSU. Nearly 60% of patients in an MSU had therapy decisions for or against thrombolysis based on diagnostic work-up, including laboratory and imaging studies, made within 60 minutes, compared to only 4% who received standard care.

A newly published study in the Journal of the American Medical Association (JAMA) conducted in Berlin between February 2017 and November 2019 also produced impressive results, with stroke victims who received MSU care having less disability after 90 days. The objective of this non-randomized controlled intervention study of 1,543 patients was to evaluate the functional outcomes at three months among patients with acute ischemic stroke who received prehospital care by a conventional ambulance or by an MSU.

Heinich J Audebert MD from the Centre for Stroke Research Berlin, Charité-Universitätsmedizin Berlin, and co-researchers reported that 80.3% of MSU-dispatched patients had none-to-moderate disability at 90 days compared to 78.0% of the conventional ambulance-dispatched group, 12.6% compared to 13.3% had severe disability, and 7.1% compared to 8.8% died.


(© Universität des Saarlandes)

Professor Klaus Fassbender MD is Director of the Neurology Clinic in Homburg, Germany.

James C Grotta MD is director of the Houston Mobile Stroke Unity Consortium, called MSUs 'a stroke centre on wheels'


(© American Heart Association)

Heinich J Audebert MD works at the Centre for Stroke Research Berlin, Charité-Universitätsmedizin

Erik Freitag MD and colleagues at the Klinik und Hochschulambulanz für Neurologie, Charité–Universitätsmedizin Berlin, provides useful recommendations in a newly published article in Stroke 'How to set up a successfully running mobile stroke unit program'. In addition to technical, staffing, and logistical requirements, they discuss if an MSU program makes sense in the area a hospital serves.

One million people catchment area for one mobile stroke unit

'We estimate a one million people catchment area to be a proper population covered by one MSU,' they advise. 'In health systems with hospitals competing for stroke cases, it's vital to start with intensive communications. MSU services can work smoothly if they are operated in close collaboration with the dispatch centre and EMS.' Allies, such as politicians, will be needed to support the system if it is to be paid by public funds. Legal issues also need to be investigated in advance.

'Organising an MSU service is not an easy task,' Freitag observes. 'But enjoy the pleasure of thrombolysing patients in the 'Golden Hour' of stroke, with many patients experiencing rapid recovery.'

Radiographers and radiological technologists ask…

Is shielding outdated?

Contact shielding is one of the most divisive areas in radiography. Whilst some believe this is essential in protecting patients from radiation, others think the risk has reduced significantly in recent years.

Report: Mark Nicholls

The 'for and against' shielding in radiography was debated during 'The Big Debate: Shielding in radiography – an outdated practice?' a session in the online ISRRT (International Society of Radiographers and Radiological Technologists) congress in Dublin this August.

Before the session, a poll of the online delegates was taken, which asked: 'Do you believe contact shielding should be routinely used for optimisation?' Just over 37% of online delegates said 'yes', 42.9% 'no', and 20% were unsure.

Introducing the speakers, debate chair Louise Rainford said guidance documents on the subject remained vague, while other advice said shielding should be discontinued for routine use.

'Where does that leave us as radiographers?' she asked. 'It leaves us very confused, but this debate is timely. The subject is very important for our profession.'

Stepping forward, Dr Shane Foley, Head of Subject for Radiography at University College Dublin, argued for an end to shielding, whilst Mark McEntee, Professor of Diagnostic Radiography at University College Cork, stated the case for retaining shielding.

Both participants drew on their own research and studies on this subject, interpreting findings to back the case for and against.

Better education and technology

In opening his case, Foley said the poll result underlined 'exactly why we are having this debate'.

In the decades since the benefits of organ dose reduction were introduced in the 1950s, the typical radiation dose delivered in radiography had dropped significantly, he pointed out. 'We now have really good equipment, much better education and technology, and the risk has come down, as have the doses we typically deliver.'

The inappropriate location of shielding is among the risks, for example obscuring the anatomy and leading to increased dose, resulting in re-takes, or interfering with automatic exposure control. Using shielding in CT scans can also cause artefacts and noise.

'In terms of the dose we deliver, and where is it coming from, the vast majority of radiation dose is in the primary X-ray beam and dose from scatter radiation is less than one per cent. Most of the scanner dose is coming from internal scatter within patient, which we cannot protect against.'

Scatter dose

The majority of scatter dose is less than 0.1 msv, Foley said, which presents the need to put this into perspective for patients and in the context of radiation that people are exposed to in everyday environments, such as from air travel or radon gas.

There are benefits and risks with shielding but he suggests radiographers should focus on alternatives, such as that collimating the beam on a radiography of the lumbar spine reduces the dose patients receive by 48%. Doing nothing on the topic is not an option, Foley warned. With the profession split only sends a message to patients that radiographers cannot agree on the evidence.

He also referred to a European consensus document that in general recommends against the use of routine shielding for most exams.

Mark McEntee is Professor of Diagnostic Radiography at University College Cork and a recognised leader in clinical translation of medical imaging optimisation and radiological perception. With more than 200 original papers in radiological journals, his publications explore novel technologies and techniques that enhance the detection of clinical indicators of disease, whilst minimising risk to the patient.

Patient choice

McEntee pointed out that placing a lead shield takes 'very little effort' but, because the risk is the patient's, not the radiographer's, patients should have a choice in this risk – which is still 'absent from the guidelines'. 'While doses may have decreased for clinical examination,' he added, 'the number of examinations people are having has increased. In 1996, 149 out of 1000 patients entering hospital had a CT scan, but by 2012 that had tripled and tripled again by 2020. Now, about a third of patients who enter hospital have a CT exam. These examinations are also getting more complex, and common examinations now exceed 50 msv.'

McEntee also underlined that even low doses are dangerous and not all patients are the same.

Systematic reviews

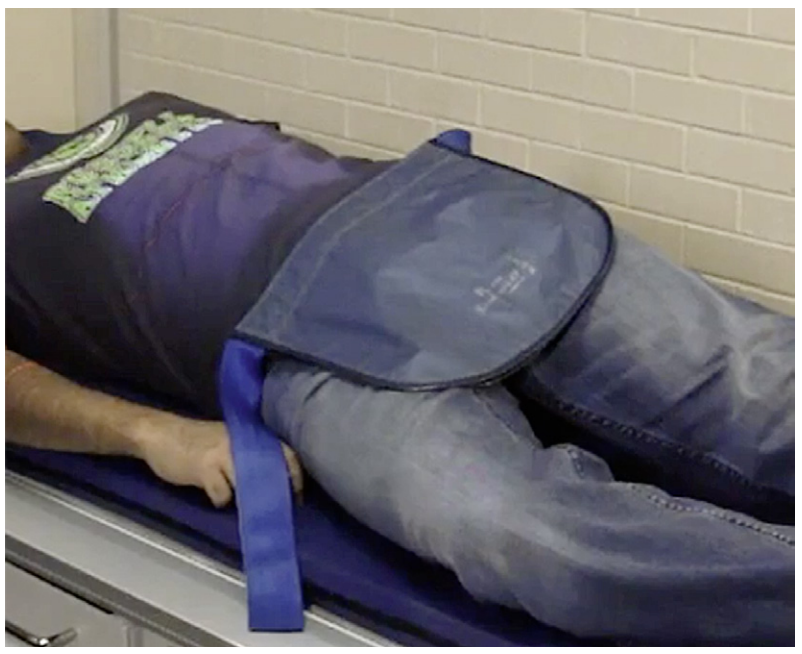
Additionally, there are patients who are at increased risk of diagnostic radiology, such as children and the carriers of BRCA1/2 mutations, where radiation can be harmful. During CTA (computed tomography angiography), he added, the breast may receive up to 24.3 milligrays (mGys) of radiation, compared to 4mGys with a mammogram. 'If we displaced the breast and add lead on top of that, we can reduce dose to the breast by 10 mGys.

'If I was a patient with that mutation, I would want that protection but we just don't know who those patients are. Lead shielding, correctly placed outside the field of view and away from the AEC, can help reduce these harms.'

He pointed to 'hundreds of papers' that demonstrate that lead shielding can reduce dose to patient.

'The evidence against using lead shielding is very weak,' he sais. 'As a profession we need to carry out our own randomised controlled trials and do our own systematic reviews. Shielding in radiography is not outdated. If it is used outside of the field, it reduces dose and it protects patients.'

Shane Foley is an Associate Professor and Head of Subject for Radiography at University College Dublin, a past-President of the Irish Institute of Radiography and Radiation Therapy, and a current Executive Board member of the European Federation of Radiographer Societies (EFRS). He is currently on the EuroSafe Imaging Paediatric working group and was the EFRS representative on the European consensus statement on contact shielding.



Lead shielding in use during an oblique kidney projection

Further research

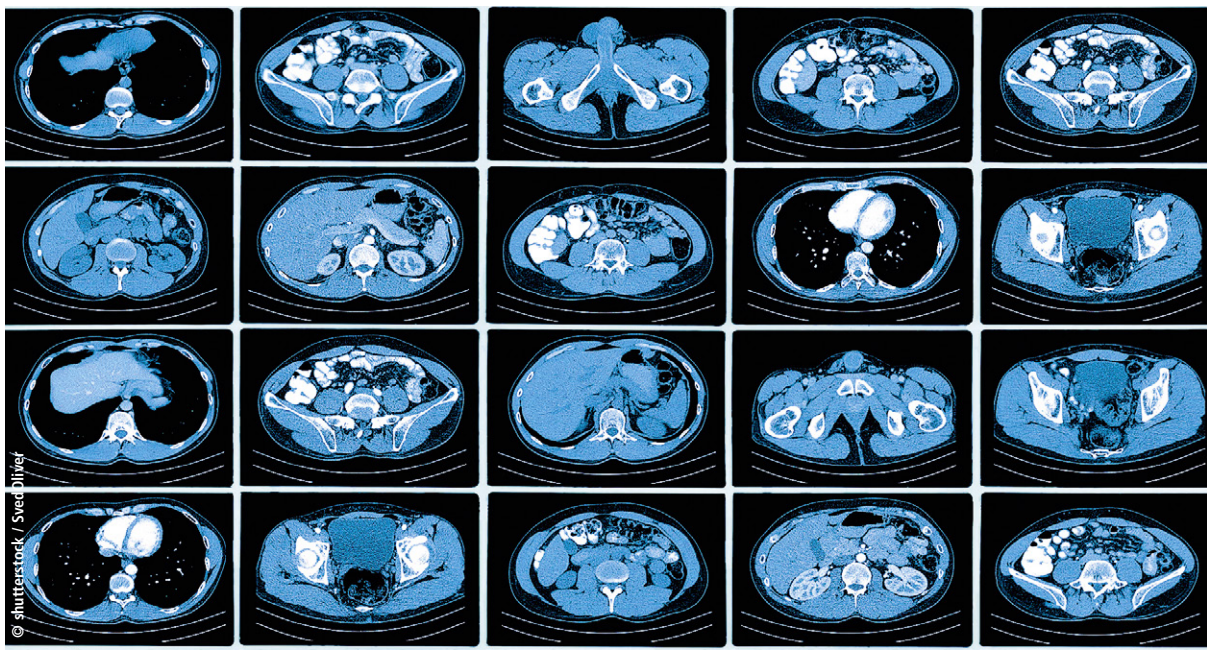
At the end of the debate, the poll was repeated and indicated a shift in position on contact shielding among online delegates with 47.2% believing 'shielding should be routinely used for optimisation', while 34.8% said not, and 18% remained unsure

What clearly emerged was the value of debating the subject, the need for further detailed research, and the importance of involving patients in the process of whether contact shielding should continue or be phased out.

'We need to drive standardisation in scanning'

Hybrid imaging is the future

During our interview with Professor Regina Beets-Tan, President of the European Society of Radiology (ESR), journalist Michael Krassnitzer asked about possible future developments in cancer imaging.



Screening exams are ever-increasing. The earlier a tumour is detected, the better it can be treated

Beets-Tan unhesitatingly pointed out that screening exams are ever-increasing and thus more and more tumours are and will be detected at an earlier stage. 'The earlier a tumour is detected,' she added, 'the better it can be treated: by resection, minimally invasive surgery, or by interventional radiology. This means we need very sensitive imaging techniques that can identify very small tumours, and also tumour growth. So we need high-resolution anatomical imaging combined with biological imaging that visualises how the tumour is behaving.

'Treatment of malignancies where the tumour has already spread to other parts of the body has also become more effective – the keywords are immunotherapy and targeted therapy. To evaluate the response of these therapies, we also need special imaging techniques that can visualise not only the morphology, but also the biology of the tumour. In addition, we want to extract as much information as possible from these images by using artificial intelligence (AI).'

Future imaging techniques

'Hybrid imaging. That's the future. It involves the combination of several techniques: First, magnetic resonance imaging (MRI), which provides high-resolution images of morphology; second, perfusion imaging, which can quantify blood flow to the tumour; third, diffusion imaging that can map the cellular architecture, which is quite different in cancer cells than in healthy cells; and fourth, positron emission tomography (PET), which can map the metabolic activity of a tumour. Combining all these methods gives the highest possible sensitivity.'

The role of imaging in immunotherapy

'Currently, imaging capabilities in immunotherapy are very limited. Computed tomography (CT) is used in follow-up scans, but this morphologic imaging alone is insufficient. Sometimes the tumour becomes larger during treatment, but this is not tumour growth but swelling due to the immune response. Therefore, biopsies have to be done regularly to find out what the response of the tumour to immunotherapy actually looks like.

'In other words, we also need imaging here to visualise the behaviour of the tumour. Specifically, we need to visualise the tumour microenvironment, that is, the immediate environment of the tumour, down to the level of the individual immune cell.'

How far developed is this kind of imaging?

'We are still at the very beginning. First, it's important to get funding for the relevant research. I'm a member of the Mission Board for cancer, an expert body that advises the EU Commission on cancer. We have recommended that the Commission invest in research into modern hybrid technologies to better evaluate the response to the new, very expensive therapies – such as immunotherapy.'

Has the initial euphoria faded about AI's potential to reveal tumours?

'AI is still a pretty promising thing. However, it has proven to be a problem that the data with which the artificial intelligence system is fed must be very homogeneous. At my clinic, a study has just been completed in which 800 MRI images of a particular tumour from all over the Netherlands have been fingerprinted by AI. The results are little better than a coin toss. That's precisely because the scans are all so different. So we need to drive standardisation. Once the underlying data is standardised, the results obtained using AI will also be more reliable.'

Professor Regina Beets-Tan is President of the European Society of Radiology (ESR) and Chair of the Department of Radiology at the Netherlands Cancer Institute.

Alongside future cancer imaging, what might arrive to advance radiology in general?

'Radiologists will play a greater role in the clinic in the future. Currently, radiologists are busy with a lot of routine tasks, which in the future can be taken over by AI, and also by less specialised and less expensive staff. The time radiologists gain when relieved of routine tasks can be put into other tasks. Why shouldn't radiologists explain their image findings to patients?

'Now that malignant diseases are being detected earlier and earlier, the need for interventional radiology will also increase. In any case, radiology must continue to evolve. We need to combine our technology with clinical expertise. If we don't, we run the risk that our specialty could one day become superfluous.'

IT system raises ...

Monitors and digital door signs

Pharmaceutical research companies espouse very high security standards because they are potential victims of cyberattacks and espionage. The biopharmaceutical company Boehringer Ingelheim, for example, ensures systems are or high standards and particularly secure.

The company runs regular security checks. One way to ensure this is to separate the systems from the office network. Each monitor is assigned a separate port, which is checked via IT security. This has helped to survive attacks without, so far, any damage.

Monitors, as essential work aids, must be secure

The IT service provider Rein Medical has been supplying these monitors since 2019. Before installation the company and its solutions also underwent a security check. In its labs and work areas, Boehringer Ingelheim relies on eight OPERION monitors with a screen diagonal of 24 inches and two monitors with a screen diagonal of 55 inches.

The monitors are only used to display information. With the 24" displays, the employees also have access to the Manufacturing Management Software (MMS), i.e., the integrated software for automatic production planning and control. They use this to centrally enter data, and to operate and control workstations and systems.

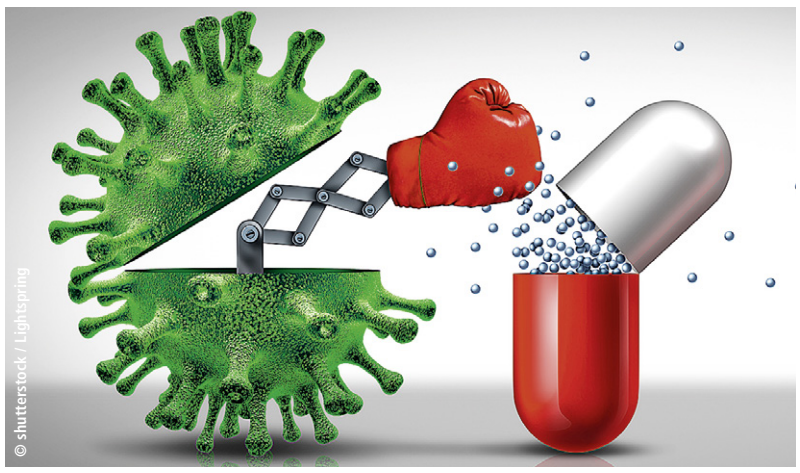
In the selection process, Boehringer Ingelheim's managers looked at a whole range of monitors from different manufacturers and assessed them based on predefined criteria. Finally they chose the solutions from Rein Medical because this company presents a broad portfolio and offers many different sizes. 'The monitors also fulfilled other essential requirements: They can be treated with commercially available cleaning agents, have a retractable keyboard and meet all fire protection requirements and other specifications of the pharmaceutical company,' the IT specialist firm reports. 'The introduction of the monitors went as smoothly as the choice of system.

The displays run efficiently. Since the terminals are connected to the room information system via a terminal server, there is only one point that needs to be maintained. The electronic door signs also perform reliably.'

Gaining back ground lost to bacteria

Antibiotic resistance in France

France consumes more antibiotics than many other European countries – almost 30% more than average. Shockingly, outpatient prescriptions are twice the number of those in Germany or the United Kingdom, countries of comparable socio-economic standing.



Interview: Jane MacDougall

As might be expected, this high rate of usage was accompanied over time by a worryingly constant increase in antibiotic resistance; at one point, for example, Escherichia coli resistance to 3rd generation cephalosporins increased every year for 10 years. However, the strict national plan in place since the beginning of the century appears to be having effect. Since 2016, there has been a downturn in resistance in both the community and nursing homes.

What is the situation today and how can we ensure this promising trajectory remains? We spoke with Laurent Dortet, Co-Director of the National Reference Centre for Antimicrobial Resistance.

Major concerns

'Antibiotic resistance is still a problem in France, but no more than in other countries. Many of our neighbours have a greater problem than France, for example Italy or Greece. Antibiotic resistance is a worldwide problem. The WHO has identified the most problematic bacteria, essentially Gram-negative organisms, the Enterobacterales, Escherichia coli and Klebsiella spp., where resistance is caused by strains producing broad spectrum antibiotic degrading enzymes, such as carbapenamases. Also amongst the Gram-negatives there is carbapenem-resistant Pseudomonas aeruginosa. These bacteria are a particular problem because the Enterobacterales cause the majority of nosocomial infections.

'On the other hand, while Staphylococcus aureus remains a significant pathogen, in France we have made major progress against MRSA over the past 20 years, from 30% to 15% methicillin resistance. That means we have halved our rate of MRSA. 'Another reason we are less bothered by the Staphylococci is because new molecules have become available giving us new therapeutic options. But for Gram-negatives our choices are much more limited. The pipeline is empty, very few molecules have come out and they are not the panacea, we don't have a miracle cure yet.'

Factors that cause antibiotic resistance

'A good antibiotic will lead to resistance because bacteria are fighting for survival. Resistance arises from a combination of factors. The most important is the overuse and/or misuse of antibiotics on a global, not individual level.

'Everything done in veterinary medicine and animal husbandry will have a knock-on effect on humans. Using antibiotics to fatten animals, pigs, chickens, etc. shouldn't be done, we need antibiotics for health. The use of antibiotics outside the hospital, in aquaculture and agriculture releases large quantities of antibiotics into the environment where they can start to build up reservoirs of resistance. This needs to be reduced.'

French strategies that work

'The Mission Spares which monitors resistance gives an overall vision of the situation. It allows us to compare ourselves with other countries to see what we are doing well or less well and, above all, to see the evolution. I think it's extremely important to follow the epidemiology of resistance, regularly. We have multiplied by ten the number of species studied by the previous mission, which I think gives a more realistic idea of the situation than we had five or six years ago.

'However, there is always a question mark over how we diffuse this information to the infectious disease specialists, to the doctors in the community to have action. This is always the difficult part, to translate data into practice. This is complicated by the fact that while we scientists gather the information, its dissemination is political. We can give our advice, for example we can say that a mechanism of resistance is emerging, but it's out of our hands.

'Decisions on antibiotics have to be coordinated and made on an international level, because if France does something and Belgium or Italy, for example, do nothing we'll never solve the problem. Hypthetically, we can say that we'll reduce the use of antibiotics in animal husbandry but China says it wants to continue to use colistin to fatten its chicken. Very quickly they'll have resistant bacteria that will arrive here even faster than Covid-19 did.'

French antibiotic resistance

'Hospital doctors are highly aware, especially those in large public (CHU) hospitals. I think the level of awareness is lower among general practice doctors, therefore we are seeing less antibiotic resistance in the community. In terms of the general public, I think they are not aware at all.'

Can we raise awareness?

'There are, and have been, many campaigns run by social security to raise awareness amongst HCPs in hospitals and the community, for example for paediatricians, to limit antibiotic prescriptions for otitis. We see this worked because the amount of resistant Pneumococus, the bacteria causing these ear infections, has reduced over the time since the campaign aired and awareness rose. Doctors now ask 'Do I need to use an antibiotic for this patient, this time?' Likewise patients need to learn not to expect a prescription every time, which is quite ingrained in the French. In other European countries, such as Denmark, it's the opposite. 'The 'antibiotics are not automatic' campaign in 2018 worked really well, but this type of campaign needs to be regular but, too many public health messages cannot be given at once and, for now, there are other priorities.'

Pharmacist **Professor Laurent Dortet** is Co-director of the Associated National Reference Centre for Antimicrobial Resistance and bacteriologist in the Bacteriology and Hygiene Department at the Kremlin-Bicêtre University Hospital, South of Paris. He completed his PhD in microbiology, then became a post-doctoral researcher at Imperial College, London, UK, before returning fulltime to his role at the Kremlin-Bicêtre University Hospital.

Possible solutions

'One thing is to offer incentives to develop new antibiotics. Developing an antibiotic costs the same as any other medicine, but the return on investment is much lower; an antibiotic is taken perhaps for a week, once in a patient's lifetime; a statin is used every day for a patient's lifetime. This is one reason we have no new molecules. If we want pharmaceutical companies to invest, we need to be inventive in ways to keep the process financially interesting, perhaps by extending patents for 30 or 40 years.

'We also need to screen rapidly, to detect where resistance is occurring. This is part of my work, developing rapid diagnostic kits to detect resistance, so we can start appropriate antibiotic therapy fast, to prevent resistance having a chance and gain back the ground we've lost to bacteria.'

security and flow

Knowing from outside what´s happening inside

'This refers to the 40 door signs that Boehringer Ingelheim has been using since April 2021. 'The customer's employees saw the digital door signs during a meeting at our headquarters in Mönchengladbach and were immediately interested,' recalls Dirk Lambertz, the company's sales representative responsible for the project. 'They were particularly taken with the LED status display, which is quite unique in this form.' They were also struck by the possibility of adding individual content to the door signs. At that time, Boehringer Ingelheim needed a digital display to provide employees with key information about rooms and equipment on site. The display also had to meet the high requirements for peripheral devices within the production rooms.

'After their cleanroom suitability had been successfully tested, the DOORSIGN displays were easily integrated into the IT infrastructure. The high flexibility of the electronic door labels was helpful,' Rein Medical reports, adding that the automation engineer regards the integrated LED frame as a particular highlight of the door signs, as well as the possibility of control via both hardware contacts and software. 'These control options are central to GxP alarms for critical products,' Rein Medical's automation engineer Thomas Jahn explains.

Data displayed comes directly from the company's internal building and room information system and is shown on the Doorsign displays. 'This gives the employees a better overview of what is happening in the laboratories and production rooms. Doorsign was easily integrated into Boehringer Ingelheim's existing IT infrastructure and offers tremendous added value by making processes transparent.'

Tried, tested and very satisfied

'The introduction of all the components went smoothly,' reflects Thomas Jahn. 'When problems did occur, we always received help quickly. We've also always been able to make an appointment quickly with the support team.'

mg fach verlage

Publisher
Mediengruppe Oberfranken – Fachverlage GmbH & Co. KG
E.-C.-Baumann-Str. 5
95326 Kulmbach/Germany
Phone +49 (0) 9221/949-311
Fax +49 (0) 9221/949-377

Editor-in-Chief:
Brenda Marsh (BM)
Editorial team:
Wolfgang Behrends (WB),
Sonja Buske (SB)
Senior Writer:
Mark Nicholls (MN), Great Britain
Mélisande Rouger (MR), Spain
Publishing Director:
Mareike Scholze (MaS)
Managing Directors:
Walter Schweinsberg, Bernd Müller
Founded by Heinz-Jürgen Witzke
ISSN 0942-9085

Correspondents
Austria: Michael Krassnitzer (MK)
France: Jane MacDougall (JMD)
Germany:
Cornelia Wels-Maug (CWM),
Karoline Laarmann (KL),
Katrin Schreiter (KS)
Dr Christina Czeschik (CC)
Spain: Eduardo de la Sota (EdS)
The Netherlands:
Madeleine van de Wouw (MvW)
USA: Cynthia E. Keen (CEK)

Subscriptions
Dorothea Fleischer, Theodor-Althoff-Str. 45, 45133 Essen, Germany

Subscription rate
4 issues: 32 Euro, Single copy: 8 Euro.
Send order and cheque to:
European Hospital Subscription Dept
Printed by: WVD, Möhrfelden, Germany
Publication frequency: quarterly

Representatives
China & Hongkong: Gavin Hua, Sun China Media Co, Ltd.
Phone: +86-0755-81 324 036
E-Mail: 627416876@qq.com
Germany, Austria, Switzerland:
Ralf Mateblowski
Phone: +49 6735 912 993
E-Mail: rm@european-hospital.com
France, Italy, Spain: Eric Jund
Phone: +33 493 58 77 43
E-Mail: jund@european-hospital.com
GB, Scandinavia, BeNeLux:
Simon Kramer
Phone: +31 180 6200 20
E-Mail: kramer@european-hospital.com
Taiwan: Charles Yang
Phone: +886 4 232 236 33
E-Mail: medianet@ms13.hinet.net
USA & Canada:
Hanna Politis, Media International
Phone: +1 301 869 66 10
E-Mail: hanna@media-intl.com
Maria Kaiser
Phone: +1 250 726 4007
E-Mail: mkads@mac.com

A potentially devasting impact on non-Covid patients

Covid-19 alters antibiotic use

The long-term impact of the coronavirus pandemic on antimicrobial resistance (AMR) remains difficult to predict, Mark Nicholls reports.

Infectious diseases consultant Professor Alison Holmes said Covid-19 has impacted on antibiotic use in hospitals and across the wider community, but more research is needed to fully assess the extent and implications.

Holmes discussed the subject in detail in her presentation 'Healthcare associated infection, antibiotic use, drug resistance and Covid-19', to the 73rd annual congress of the German Society for Hygiene and Microbiology, with a focus on bacterial infections, antibiotic use, hospital-onset Covid infection and how that should be tackled, and healthcare associated infections (HCAI) in individuals with and without Covid-19.

'Bacterial infection and Covid-19 were a major concern, particularly at the beginning of the pandemic in terms of driving antibiotic use and potential AMR,' said Holmes, Professor of Infectious Diseases and Director of the NIHR Health Protection Research Unit in Healthcare Associated Infections and Antimicrobial Resistance, as well as and the Centre for Antimicrobial Optimisation (CAMO) at Imperial College London.

Antibiotic prescribing

Emphasising the importance of looking at the effect, directly and indirectly, of other clinical activity related to infections on Covid and non-Covid populations, Holmes said: 'There were many consequences that could impact on infection that could fuel antimicrobial resistance, or indeed reduce it significantly, and it is important that we consider this across multiple levels.' Further considerations included the potential for bacterial infection risk on new therapies, particularly immunological; the pressures on different healthcare systems, and patient backlogs.

Holmes, who has contributed to the national Covid-19 response in the UK, noted that early in the pandemic, experts were keen to conduct a rapid review in terms of bacterial and fungal infections, but particularly how it could support antibiotic prescribing.

Initial research

Low levels of coinfection in Covid-19 patients (8%), but high rates of antimicrobial use (70%), were suggested in initial research, but there were research limitations: studies often did not differentiate whether patient populations were in critical care or not; there was limited microbiology, risk factors such as whether patients were being ventilated were not reported; and complications of excessive prescribing were not identified. She said the evidence at the time supported use of antibiotics only in suspected or confirmed serious infections and with regular review, short duration and the need to maintain strong antimicrobial stewardship programmes, although more recent evidence has 'expanded the level of understanding of co-infection'. Critical care has been highlighted as the main focus for coinfection, with organisms linked predominantly to local epidemiology. However, while the majority of coinfections were hospital-acquired pneumonia or ventilator-associated pneumonia, there was a need for these risk factors to be collected in a standardised way to 'understand risk of Covid in terms of coinfection'.

Non-Covid patients

More recent study findings, however, were not dissimilar to the early research, with 8.6% of bacterial infections seen versus 74.6% of patients on antibiotics.

But she added: 'We are not doing well enough in terms of understanding what is going on in low resource settings and we need to do much better around that to understand the potential devasting impact this is having on our non-Covid patients.' Holmes also discussed the impact of Covid on bacteremias, notably a major drop across the two waves of Covid and particularly in e.coli bacteremia, though this was tempered by the change in the patient mix.

In the USA, she noted, there was a rise in hospital-acquired infections in 2020 compared to 2019, after years of reductions, mainly catheter-associated urinary tract infections, ventilator associated events, and MRSA, but notably no increase in surgical site infections (with surgery being cancelled), and no increase in C.diff rates.

Community prescribing

With concerns about AMR in acute care, the implications of a fall in antibiotic use in the community – traditionally an area of higher usage – remain uncertain. 'That's a major concern because we don't know if people could access treatment appropriately, or if patients with infections are going untreated. There is a need for better evidence on this,' Holmes said and emphasised the need for 'strong, robust surveillance' of hospital-onset Covid for future pandemic preparedness, and recovery of healthcare resilience and safety. Health systems need to understand that non-Covid patients can be well looked after and health systems be run effectively and safely with the appropriate level of capacity in terms of beds and staffing, she underlined.

Local epidemiology

While bacterial infection in Covid patients is relatively low, with the majority in acute care due to HCAIs, she said understanding the local epidemiology is critical and that a strong foundation of effective prevention and control practice is vital.

Antibiotic stewardship is also crucial given the high rates of prescribing, and there is a need for a better framework for prospective reporting to inform clinicians in providing safe healthcare for HCAIs associated with Covid, for hospital-onset Covid infections, and for antibiotic use within the Covid pandemic.

'By recognising that the AMR pandemic is happening already, we need to be able to understand and make the most of the information, so that we can learn from the Covid pandemic,' the professor said.

'The long-term impact of the pandemic on AMR is still difficult to predict and it's important to have a whole health system perspective, looking at what is happening in the community and in acute settings at the same time.'

© Imperial College Healthcare / NHS

Alison Holmes is Professor of Infectious Diseases and Director of the NIHR Health Protection Research Unit in Healthcare Associated Infections and AMR, as well as the Centre for Antimicrobial Optimisation (CAMO) at Imperial College London. She leads an international, multidisciplinary infectious disease research programme focusing on optimising antimicrobial use by developing innovative approaches and technologies to manage and prevent infections.

© shutterstock / Jarun Ontakrai

Covid-19 has impacted on antibiotic use in hospitals