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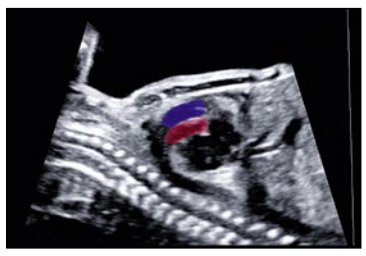


Drones take laboratory logistics to a new level

A Swiss hospital group is using drones to fly medical laboratory specimens between its key centres, Mark Nicholls reports

Luca Jelmoni became CEO of the two public 300+-bed hospitals in Lugano, Switzerland (Ospedale regionale di Lugano) in 2012. He graduated from the ETH Zurich (Swiss Federal Institute of Technology) in 1992 and gained his MBA from Kellogg University in Chicago, USA. Initially he worked in the pharmaceutical industry, then in retail, business development and corporate finance. In 2007 he became CEO of a leading Swiss clinic specialised in reproductive medicine.

In what is believed to be a world first, the eight-hospital Ticino EOC organisation has partnered with Swiss Post and US drone manufacturer Matternet to spearhead faster, more efficient specimens transport. The trial is being held for flights covering the 1.3 km between two of its Lugano hospitals, the Ospedale Civico and Ospedale Italiano.

While each hospital has its own emergency room and laboratory, the laboratory at Ospedale Italiano, in the city centre, closes at 5pm and at weekends. 'Presently the blood samples are transported between the two hospitals by local taxis,' explained hospital director Luca Jelmoni. 'This is, of course, subject to the availability and to traffic conditions. Therefore, to ensure transport that's always available and economically more interesting, we decided to apply the new technologies and use drones to transport our blood samples in those time slots when one of the laboratories is closed.'

There are already clear benefits from using drones in this way: the transport time does not depend on traffic conditions or third parties, cost is lower than by taxi, and the drone can fly over hills and mountains, considerably reducing the length of transportation compared to the road.

In addition, when snow makes road driving more difficult, drones will still operate and avoid delays in delivering specimens and test results. Whilst the distance between the hospitals is relatively small, Jelmoni told European Hospital that the drone can actually fly as far as 20 km, which means Ticino EOC is already considering a future possibility of transporting laboratory samples from other hospitals even further away.

The first phase of the initiative involved proving the technical feasibility and acquiring official licenses and permits for the autonomous flights over populated areas, and this has been completed. With the approval of the Federal Office for Civil Aviation (FOCA), the trial will now move to the second phase later this year, which will see drone transport integrated into the hospital processes.

'That will be to test the integration of drone transport with the emergency room and laboratory processes,' Jelmoni explained. 'This will be supported by a specific device, being developed by the supplier, which will autonomously load and unload the drone and charge the batteries.'

Phase three will see day-to-day usage of drones to transport blood samples between the hospitals, with hospital staff launching the drone via a smartphone application. The drone will then fly autonomously along the predefined route to its destination, where another staff member will receive the box.

Some observers have raised concerns that the acceleration and movement of drones might affect the quality and integrity of blood samples but, in a separate study conducted at John Hopkins University in Baltimore, researchers have shown this is not the case.

The Matternet logistics drone used in Lugano is a quadrocopter, 80 cm in diameter (without rotor blades). Able to carry up to 2 kg, and with a top speed of 36 kmh, the drone can operate in temperatures of -10 to +40°C and at an altitude of 50-100 m above the ground.

Safety features include a parachute in case of total drone failure, but all the drones' on-board critical components are replicated in case of malfunction.

However, the test phase has seen more than 80 flights without any problems and the hospital believes transportation with drones will be as secure as transportation with a taxi. Once the drone meets all the strict requirements regarding safety, practicality and reliability, they will be in daily use between the two Ticino EOC hospitals – some time in 2018.

www.healthcare-in-europe.com

Nantes CHU – designed to fit 21st century medicine

Opening in just under a decade

Report: Jane MacDougall

21st century challenges are multitudinous for all. Ageing populations, a changing disease burden; increasing obesity with associated morbidities – Type 2 diabetes, cancer and cardiovascular disease; climate change pressures and more. Any new build plan demands a low carbon footprint; respect for the environment is paramount.

To capture all those elements, the plan to regenerate a previously 10 hectare industrial site on the 'Ile de Nantes', a central region of the largest city in Western France, by creating a 'Healthcare zone' is exceedingly ambitious.

Since 2015, when the choice of architect was made, the initial planning stage has involved the input of more than 850 people from the key areas concerned. In the two years since the project was first mooted, over 150 meetings have taken place between the 57 different working groups involved. Each group is always headed by a trio of medical, ancillary and administrative staff and held in the presence of the architects. More than 1,200 modifications were made before the final plan was made public in June 2017.

Central to the hospital's architecture is the ease of the patient's journey through the hospital. Medical professionals and patient user groups have been working together to produce the best possible patient journey, which provides the ability to exchange medical information and ensure the correct care at the right time.

Patient groups have also been consulted to understand their major wishes in terms of privacy and patient confidentiality, reduction of waiting times and so on. Within this framework, the need for an agreeable working environment for the many hundreds of professionals who will be based here every day cannot be ignored.

Using the mantra 'high technology and humanity', the project has objectives to provide healthcare, teaching and research on a human-scale at the heart of the community it serves.

In practical terms, the new hospital will serve to re-home the current hospital group, which includes the medical and surgical obstetrics capacity of the Hôtel-Dieu and North Laennec Hospitals, as well as their emergency and ambulance services. Space has also been planned for the eventual inclusion of the René Gauducheau Oncology Institute and teams from the highly respected medical university research centres (DHU), which cover specialties such as thoracic medicine, digestive tract medicine, immunology, nuclear medicine, kidney transplantation, etc.

The new hospital has been conceived with the knowledge that medicine is evolving. This future has been considered for planning under four 'Ps' – prevention, anticipation of risks and programmes to modify behaviour; prediction, the

USA nurses augment their role in hospital care coordination

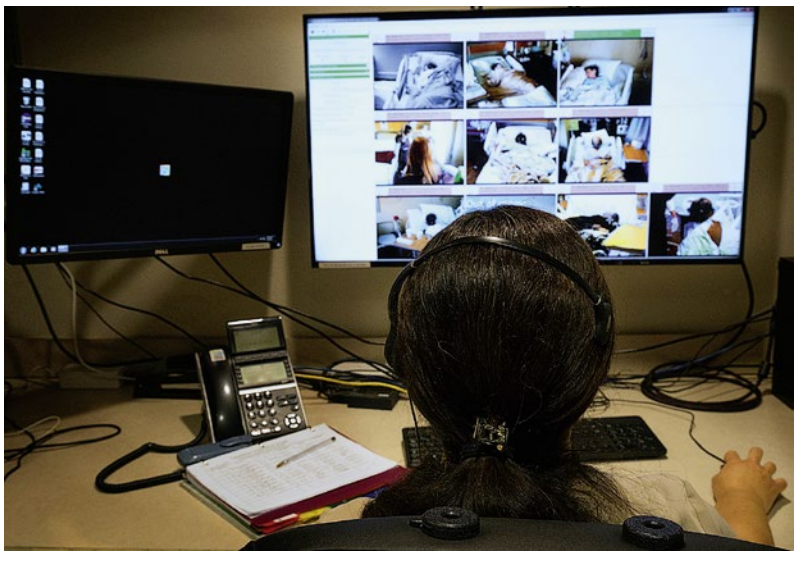
Improving patient experiences

Report: Lisa Chamoff

A nurse-led team has worked for three years to reorganise the electronic health records system at the Carolinas HealthCare System, a large healthcare organisation in the state of North Carolina, with more than 900 locations and 7,600 licensed beds.

Becky Fox, who spearheaded the effort as the health system's chief nursing informatics officer — a growing specialty in nursing, though a relatively rare position for a hospital — noted that by making the EMR workflow easier to use and reducing unnecessary documentation, they could eliminate an estimated 18 million clicks and decrease the time it takes for nurses to do a head-to-toe assessment of patients by about 20 percent, resulting in a return of 35,000 hours of nursing care.

'There is a clinical informatics coordinator at each facility and some have been nurses,' says Fox, who has a background as medical surgical nurse and had stints in the emergency department, cardiac care and was a clinical nurse specialist before transitioning into her information technology position. 'They really need to have a foot in both worlds – in the clinical world and the informatics role.'



Hospital nurses in the USA have always been the providers of direct patient care but, as the healthcare system there undergoes rapid changes, they are increasingly working behind the scenes, improving hospital technology and making key purchasing decisions, as well as preventing medical errors, improving patient satisfaction and reducing hospital admissions and readmissions by helping to improve population health.

Hospital nurses may now ensure a patient has the essential tools to recover at home, thus preventing a return to the hospital, and run programs to help ensure those in the community are leading healthy lives and receiving the proper preventive care.

'The question is not going to be, "What does the doctor do; what does the nurse do; or what does the social worker do?"' Fox says. 'It's going to be, "What is the best thing to do for the patient?"'

In the state of Texas, at JPS Health Network, nurses helped select a monitoring system for observing patients at high risk for injury, such as those with behavioural health issues, or elderly patients who may fall if they get out of bed, instead of paying a staff member to sit with the patients and watch them.

After installing the system, which provides video observation and a way for nurses and patients to communicate, falls decreased 13 percent during the first seven months of 2016 and more patients could be monitored.

'For any purchases, you're going to want the nurses' input,' says Trudy Sanders, vice president, patient care services at JPS Health Network. 'Those are the users of the equipment.' After the passage of the Patient Protection and Affordable Care Act in 2010 and the transition from a volume- to a value-based system caused consolidation in the healthcare industry, nurses have had a bigger role in care coordination in the USA's hospitals.

Becky Fox is the Chief Nursing Informatics Officer at Carolinas HealthCare System in Charlotte, USA.

'There has always been some form of case management in hospitals,' adds Seun Ross, director of nursing practice and work environment for the American Nurses Association. 'As hospitals are consolidating, nurses are managing a patient from the moment they hit hospital doors.'

Nurses also play a key role in ensuring high patient satisfaction scores, which are tied to Medicare reimbursement. 'It's everyone's job to make sure a patient has a good experience.' the Chief Nursing Informatics Officer underlines.

use of genetic and other biomarkers for the early diagnosis of disease or risk; personalisation, the adaption of treatments for the individual and participation, the active involvement of patients in their care in terms of treatment choice and new technologies. As all four areas are rapidly changing considerable forward thinking is necessary.

To meet changes in healthcare provision, 64% of surgery will be performed in a day-patient setting, compared to 55% today. This reflects the adoption of robotic and keyhole surgical procedures that are less invasive than traditional methods and shorten patient recuperation time and therefore subsequent hospital stay. The rise of chronic diseases means patients may need regular visits to the hospital to monitor the progress of their disease, possibly being treated by different specialists in different services. This requires good interconnectivity between departments and access to digital patient records while respecting privacy and confidentiality.

All departments are linked in an intelligent manner and are easily accessible for patients on stretchers or in wheelchairs; gone are the interminable hospital corridors of the 20th century.

KEY POINTS

- Scheduled opening 2026
- Work starts 2020
- 225 000 m² building surface on a 10.1 hectare site
  - 384 beds (257 ICU)
    - 100% individual rooms
  - 58 operating theatres
    - 64% day patient procedures
  - A&E capacity 130,000 patients/year
- Budget 953 million euros
- Architectural/Management team: Art & Build Architect, Pargade Architects, Artelia and Signes Paysages.

The buildings are low rise and welcoming, designed to blend into the city environment incorporating a wide central walkway.

Respectful of modern building regulations while preserving functionality, the building design offers remarkable energy performance. The structure adapts to climatic changes while the use of renewable sources allows reduced energy consumption and low carbon emissions. Each building has a control panel that records its use of energy, water and medical fluids.

All are under video surveillance and have the latest in fire prevention and control systems, their maintenance and control carried out at a distance. The hospital controls its emissions, water consumption and waste production.

Obviously, a project of this size would not be possible without consultation and commitment from the city and regional government. The infrastructure of the entire region will be impacted and incorporated; already two new tramlines have been agreed to improve access to the hospital site.

However, as the date for the first stone to be laid is still three years away there is little doubt that further changes will be made between the new public consultation phase (September 2017) and the opening date in 2026.

Defining work practices for 57,000 employees

The growing role of a hospitalist

New words are consistently spun out in the USA and frequently assimilated into 'American English'. Take the term 'hospitalist' (little used in European English), which was coined by the renowned academic physician Robert M Wachter (University of California, San Francisco) and his colleague Lee Goldman, in an article published in the New England Journal of Medicine in 1996. Lisa Chamoff unravels its meaning and the role of a hospitalist in the US today

Hospital medicine is considered the fastest growing physician specialty in the USA, with more than 57,000 'hospitalists' employed across the country. A hospitalist can loosely be described as a doctor who only treats hospitalised patients.

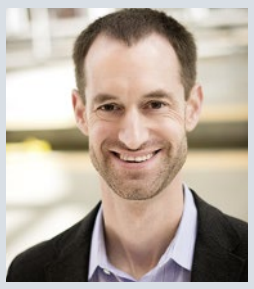
The specialty has replaced the traditional model, in which a doctor has appointments with patients in their office during the day and visits patients in the hospital either early in the morning or in the evening. Hospitalists are either employed directly by hospitals or are part of hospital medicine practices.

'A hospitalist model was developed in part to devote practice to acute care,' explains Brian Harte MD, president of Cleveland Clinic Akron General in Ohio and past president of the Society of Hospital Medicine. 'From a clinical and financial standpoint, it's difficult to manage a practice where you work in an office and manage patients in the hospital.'

As facilities look to improve patient outcomes, hospitalists are on the front lines. At the University of Colorado, Denver, which has one of the oldest and largest hospital medicine programs in the country with 60 physicians, the facility found that under the hospitalist model, the length of stay was a day shorter than the more traditional models of care.

Read Pierce, interim director of the Hospital Medicine Group at the University of Colorado, Denver, says consistency is key in taking care of acutely ill patents. 'That's a major factor because you're able to make decisions more quickly and make evaluations more quickly,' he says.

Dr Luci Leykum is division chief of general and hospital medicine at the University of Texas Health Science Center in San Antonio, USA.



Read Pierce has served as interim director of the Hospital Medicine Group at the University of Colorado, Denver, USA, since 2015.

Brian Harte MD became president of Cleveland Clinic Akron General in Ohio, USA, in September 2016.

While the hospitalist movement took off earlier in the USA, Pierce says the United Kingdom has a similar version of a hospital medicine program – when someone is in the emergency room for four hours, they go under a hospitalist's care. Recently, programs have also been deployed in the Middle East and Singapore, he points out.

Hospitalists tend to also take on key hospital leadership roles, as they become experts in how to make a complex system work better, he adds. They help shape policies to reduce preventable readmission rates, hospital acquired infections, accidental falls and to promote antibiotic stewardship.

'Over the last five years,' says Harte, 'I've noticed more and more hospitalists being promoted to leadership roles, in large part because of their developing expertise in both leadership skills and systems improvement.'

Dr Nasim Afsar, the president-elect of the Society of Hospital Medicine, helped enact a rapid review process for patients who have died in the hospital, Harte says. At Cleveland Clinic, hospitalists are implementing changes in observation units.

Best practices for hospital medicine programs are evolving. There are some instances where it will make sense for a patient to remain on a surgical service because of that doctor's expertise, Pierce adds.

In general, surgeons are busy and hospitalists can help manage other issues that may be related to their hospital stay, such as a cardiac patient who has diabetes, says Dr Luci Leykum, division chief of general and hospital medicine at the University of Texas Health Science Center in San Antonio. They can also take a closer look at a patient's home situation and have a better idea of how it relates to their clinical condition than a hospital social worker would.

'You have someone there taking care of the patient and looking at their entire picture, not just the disease or procedure,' Leykum says.

Schedules are also evolving as hospital medical programs balance providing continuity of care while allowing physicians to have a work/life balance. Some doctors may prefer seven 12-hour days on and seven days off, but that schedule may not work for other physicians, Pierce points out.

Hospitalist programs also need to work out the best financial agreement with a hospital. Some hospitalists see enough patients to pay their salary, some receive a set salary from the hospital and others receive pay-outs by meeting certain achievements.

It is also important for hospitalists to work well with hospital staff. A few years ago, Leykum's facility implemented a collaborative care model in which all providers spend more time together at the bedside. They also promoted discussion in areas where they had had disagreements, such as what to do with infected hardware implanted during spinal surgery or hip and knee replacements. Hospitalists, infectious disease specialists and surgeons came up with a consistent practice. Leykum: 'We really try to increase collaboration among disciplines.'

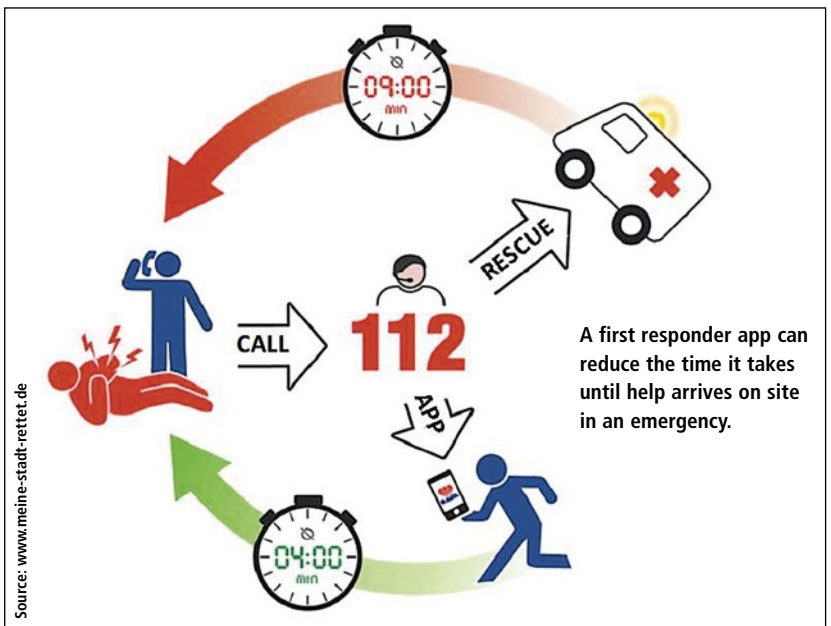
App accelerates first responders' deployment

'Shareconomy' technology enters patient care

Point-of-care diagnostics (POC) has been established for 20 years. Comprehensive smartphone coverage and 'shareconomy' technology are now helping to push the development from previous business models towards a point of patient model. The question is whether medical apps will have the same benefit as those employed for everyday use.

Dr Christian Elsner, Director of the University Hospital Schleswig-Holstein (UKSH), presented his findings on the subject of first responders at the POCT Symposium in Munich. 'The first responder figures in Europe vary a lot. Four years ago, the figure for Germany was only 25%. Now it's 31%, but we obviously want to increase it still further,' he told our *European Hospital* correspondent Anja Behringer.

In each emergency case where resuscitation is required, first responders should intervene within a matter of minutes. 'There are different concepts to achieve this, such as increasing the availability of defibrillators, telephone support for resuscitation, or the utilisation of first responders who are alerted via our app,' Elsner explains.



Source: www.meine-stadt-rettet.de

A first responder app can reduce the time it takes until help arrives on site in an emergency.

Methods – A first responder app and emergency unit plugin can locate app users near an emergency potential sudden cardiac arrest. This allows the emergency medical dispatcher to call for additional help alongside the primary rescue chain, if feasible. The UKSH also recruited qualified medical (semi-) professionals with knowledge of CPR, and a comprehensive medico-legal evaluation and guideline development were also undertaken. An atrial fibrillation (AF) app was then developed which can test for atrial fibrillation via the standard flash-LED through the app users.

Results – A clear-cut SOP and medico-legal evaluation were developed and implemented for the first responder app in a partnership with the city of Lübeck. Most of the budget (42%) had to be spent on the medico-legal evaluation and the obstacles presented by legal standards and data security, with the second largest amount spent on the socio-political discussion on how to implement the technology. User recruitment was successfully carried out via 1:1 marketing and viral marketing. After 12 months, more than 380 people were recruited as CPR lay people, with most of them already being pre-qualified. In the first eleven real cases for the app, 36% of the first responders arrived on site more than three minutes before the emergency rescue vehicles. 'It used to take 9-12 minutes before emergency staff reached the patient once the alarm was raised, but our dense network has now reduced this to 1-3 minutes,' Elsner points out.

A test study protocol for the atrial fibrillation app was developed and is being implemented in a primary AF (patients aged over 65) and secondary AF (patients after ablation) screening population. The use of this app is being discussed with health insurers and various hospitals, with a medico-legal evaluation still in progress.

The managing director of the German University Hospital Schleswig Holstein, Lübeck Campus (turnover €300+ million) since 2010 and, from 2015, managing director of its Out-patient Care Centre, **Dr Christian Elsner** is also acting director of the Diagnostics and Radiology Centre in the Kiel Campus. He is also Assistant Director of the Hospital Manager degree course at Kiel University. In the past, Elsner was Division Manager for the consultancy Pharma, Healthcare and Medical Technology in Munich, Germany, (2006-2009). Elsner is a member of the board at the European Heart Rhythm Association (EHRA).

Conclusions – Point of care testing can receive impulses from the market trends of 'shareconomy' and mobile internet technologies. Completely new business models and use cases must be discussed and must seem feasible in a first proof of concept. Achieving these new use cases will take great effort and require a lot of energy, time and money to be invested in a combination of social, legal and medical evaluations, in close cooperation with the technological development of such apps. The findings from the two use cases and field tests should give first insights on how to proceed and which problems to tackle.

Utilising potential where it presents itself

Big data in the laboratory

Useful IT tools are abundant in today's laboratories – ranging from software to evaluate analyses to specialist software for quality control, and middleware linking different devices. However, all these tools generate data, the adequate utilisation of which is not an easy task, said Udo Margraff, CEO of Laboratoires Réunis in Luxembourg, during our European Hospital interview. Among other issues, data protection proves to be a limiting factor, with the meaningful use of big data falling by the wayside.

Report: Marcel Rasch

'The laboratory has always been very focused on IT,' Udo Margraff points out. 'With around 400,000 analyses per year, we generate around five million medically validated results. However, this is just a part of the data packet. Every analytical result we release additionally contains countless data on the traceability of samples.

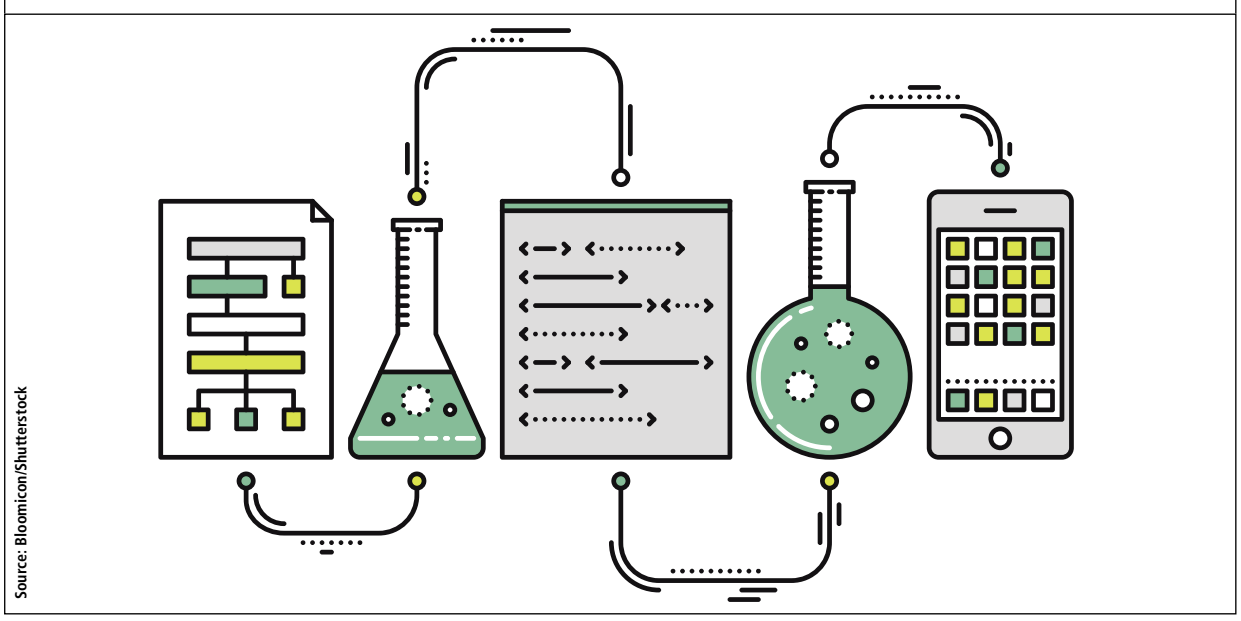
This could be the date the sample was taken, specific data for the validation of the laboratory results, the clinical anamnesis, any possible difficulties encountered when blood was taken etc. Altogether we generate up to 100 million data sets in our IT system that the doctor doesn't even get to see – and these are just the figures from our relatively small, private laboratory.'

All data is evaluated for different processes. 'If, for instance, we receive feedback from the doctor that the potassium levels of a sample are too high, we test for the cause,' the CEO explains. 'We investigate how the sample was transported, or whether there was a problem with the centrifuge or reagents. These analyses are incredibly complex but of no interest to the referring doctor as long as they receive the reason for the increased levels.'

To Margraff, statistics and studies are additionally available tools for statistical evaluations in light of the data volume. Unfortunately though, big data analyses entail two major difficulties, as Udo Margraff admits: 'Everybody talks about big data, but ultimately this data cannot be utilised in the best possible way we like to imagine.

'It is no longer a big problem to obtain validated data due to certifications and standardisations. We have a lot of very good data available. However, this requires software in surgeries and hospitals to be well maintained. The big problem is the consolidation of this data for adequate evaluations, and we are only just starting out here.'

A Canadian-Chinese research group, for instance, has been able to prove a connection between a lack of vitamin A and Alzheimer's disease. 'Many Alzheimer's patients have a lack of vitamin A, which suggests a link,' says Margraff. 'I therefore wanted to correlate these results with data from our laboratory, but out of the 2,600 eligible results from the last three years only a few hundred correlated with the respective statistics. This is not enough for a statistical evaluation. We lack the clinical patient data required to carry out such studies.' Making validated statements for publications and studies is therefore almost impossible.



Source: Bloomicon/Shutterstock

Studies like this would be very interesting for health insurers, especially with a view to prevention. 'Prevention should begin in childhood, with a healthy diet. Laboratory data is also of interest for research into prevention with regards to next generation sequencing in genetics or the microbiome: Diabetes, cardiac disease, autism, Alzheimer's disease and multi-resistance are all areas where good studies could facilitate fantastic preventative work,' Margraff emphasises.

When it comes to big data analyses, cost is also a big factor because, he underlines, 'laboratory diagnostics is expensive, therefore not utilising the data adequately is a shame. Laboratory and imaging diagnostics play a central role in medicine: 60-70% of all diagnoses are made with the help of the laboratory or imaging.'

The Agence eSanté founded in Luxembourg is the first eHealth authority to establish itself in the EU. 'I hope we will succeed in setting up a server for laboratory data that consolidates all relevant data, making data processing for publications and studies, and those on prevention, epidemics, and infections more efficient and effective,' Margraff hopes. However, in this, data protection is proving a big obstacle.

'Only by anonymising and standardising data can we satisfy data protection regulations,' Margraff points out. 'But, I'm hopeful that we will find a solution for the future. Transregional data usage is also of interest for everyone against the backdrop of cross-border healthcare. There is a growing trend towards people living and working across, and without, borders.'

'It's popping up everywhere. Is this a good thing?'

Bring your own ultrasound

Pocket ultrasound accelerates diagnosis at the point-of-care reducing the role of the radiologist, John Brosky observes

Courtesy of Sonosite

You can buy a pocket ultrasound probe online, download an app to your smart phone and start making your own diagnoses of joints and organs.

'It's popping up everywhere. But is this a good thing?' asked Michael Bachmann Nielsen, a radiologist at the Rigshospitalet in Copenhagen, during a session dedicated to handheld ultrasound at the European Congress of Radiology (ECR).

Helmut Prosch, a radiologist with Medical University of Vienna, added that pocket probes are 'used by many, but understood by few. As radiologists we don't see the usefulness of these devices, yet we are surrounded by colleagues using them.'

The chairman of the special ECR session, Michel Claudon, from the University Hospital in Nancy, France, suggested: 'Our goal is not to stop people from buying, but to train them in how to use their device.'

Quick answers to specific questions

Point of care ultrasound (POC) exams can quickly answer a specific clinical question, to send patients along care pathways rapidly. Examples of already established exams include focused assessment with sonography in trauma (FAST), bedside lung ultrasound in emergency (BLUE), and the focused echocardiography in emergency life support (FEEL).

The handheld portable ultrasound device segment is expected to be the fastest-growing niche in the overall ultrasound market, increasing at a 13.1% compound annual growth rate through 2022.

Enabling the trend toward pocket ultrasound is the wide acceptance in healthcare for bring-your-own-device (BYOD).

Changes in device design

According to a study by IT network provider Cisco Systems Inc, based in San Jose, California, by 2013 some 88% of healthcare workers used their smart phones or tablets at work, with the tacit agreement of their institution.

This has led to a key shift among device design to throw out dedicated ultrasound viewers and enable scans to be viewed on personal BYO devices, which most often have a higher resolution of the image.

Bachmann Nielsen provided an overview of the leading devices used in the western world, noting he did not include the surge in such devices coming out of Asia.

Device overview

The Vscan from GE Healthcare is one of the original devices in the segment, and the company holds the leading market share. The 14-ounce Vscan Extend is the latest version, introduced in 2016 with a five-inch touch screen for the dedicated viewer a permanently attached probe. The Vscan Extend offers, in a single handle, dual transducers, a phased or linear array enabling either shallow views of tissue or a deeper look into organs.

In 2014, Philips Healthcare introduced the Lumify smart-device ultrasound that is compatible with any handheld computer or phone running the Android operating system. The commercial USA launch came in 2015.

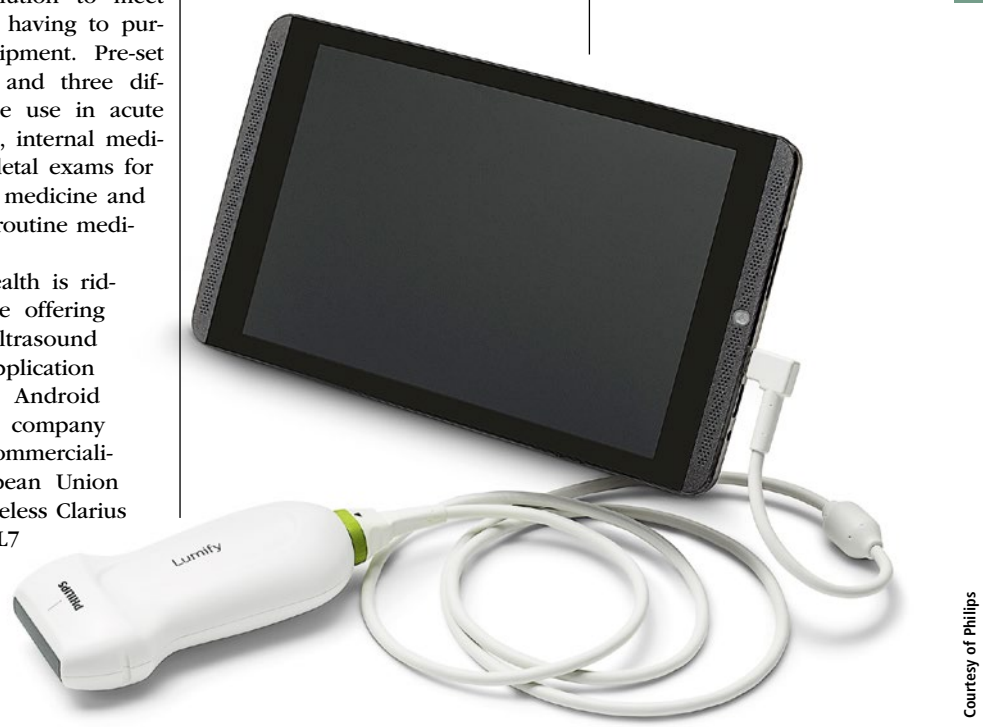
Courtesy of GE

The BYOD approach offered by Philips includes a subscription model for $199 per month for qualified healthcare professionals to scale their ultrasound solution to meet their needs without having to purchase imaging equipment. Pre-set exams in the app and three different probes enable use in acute and emergency care, internal medicine, or musculoskeletal exams for orthopaedics, sports medicine and podiatry, as well as routine medical office practice.

Clarius Mobile Health is riding the BYOD wave offering the first mobile ultrasound scanner with an application for both iOS and Android devices. At ECR the company was launching its commercialisation in the European Union of the handheld, wireless Clarius C3 and the Clarius L7 multipurpose ultrasound transducers that talk to the everyday technology onboard personal, off-the-shelf smart devices. 'We take advantage of the latest screen technology available on mobile devices, which has an appeal for radiologists with the high quality resolution and display,' said Neena Rahemtulla, the vice president for marketing.

Fujifilm SonoSite offers the iViz, a seven-inch tablet with two cabled transducers that stands out for its one-hand navigation of the touch screen and a superior 1900 by 1200 pixel image user interface, though it is hefty at 20 ounces.

Mobisante offers the Mobus SP1 System viewer that weighs less than 12 ounces as a dedicated system of transducer, cable and viewer, but also introduced the Mobius PE, that can run on any Windows-based device.

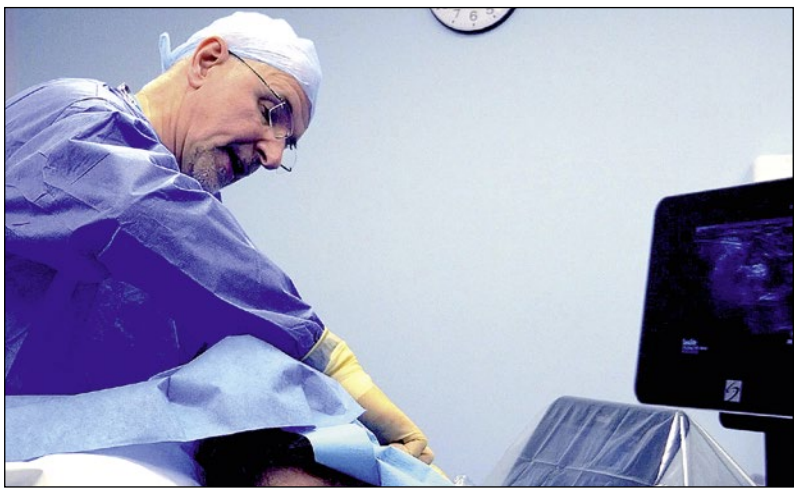


Courtesy of Philips

Regional anaesthesia is quicker, safer and m

Point-of-care ultrasound

Ultrasound guidance has proven invaluable for the regional neurosurgical centre at the Salford Royal Hospital, helping to improve safety, save time and enhance the patient experience. Here, Jim Corcoran, consultant neuroanaesthetist and clinical director for perioperative care at the hospital, outlines the uses of this technique.



When I joined the Salford Royal in 2006, my initial interest in ultrasound grew out of a need to alleviate the delays experienced by trauma patients needing a cardiac echo. Training opportunities for regional anaesthesia in the North West were very limited, but we realised that training clinicians to use point-of-care (POC) echo could significantly reduce delays in excluding aortic stenosis. At the same time, we took the opportunity to introduce training on the use of ultrasound for regional anaesthesia.

Interest in this field has grown considerably since then, and for the past nine years we have worked with Fujifilm SonoSite to run twice-yearly courses in ultrasound-guided regional anaesthesia.

Before ultrasound guidance became commonplace, regional anaesthesia was performed using nerve stimulators. Although this worked, the procedure wasn't slick. Ultrasound offers an improved way of administering the anaesthetic, which is quicker, safer and more comfortable for the patient. It allows you to visualise the nerve, giving assurance that the needle is correctly positioned, and gives you confidence that the block will work; there is always a degree of uncertainty if ultrasound is not used.

We can also dramatically reduce the amount of anaesthetic used with ultrasound-guided procedures, decreasing the likelihood of side effects. Whereas previously 30 or 40 ml of anaesthetic would be injected – because it was hard to target a specific area with certainty – you now know exactly where the needle is, and can see the anaesthetic spreading across the area. As a result, as little as 10 to 20 ml of anaesthetic is required, which is a huge reduction.

Today, we use ultrasound-guided regional anaesthesia for both awake surgery and analgesia, for example, interscalene blocks for patients having shoulder surgery under general anaesthesia. Regional anaesthesia has totally transformed shoulder surgery, significantly reducing the length of patient stays. Ten years ago, patients were admitted for one or two days, but subacromial decompressions, for example, are now treated as day cases, and even a shoulder replacement is only an overnight stay.

I also use ultrasound to place catheters in some of the more challenging shoulder replacement cases, which makes a big difference; the interscalene groove is a difficult area, and knowing the exact location of the needle is really important.

The efficiency of our hand sur-

Versatile invention tackles several routine exams

4G CMUT – opening the door to the next stage in ultrasound

Holding Hitachi's newest ultrasound probe in your hand, it looks and feels like any other ultrasound transducer. 'Yet, you are actually holding a marvel of ultrasound engineering, a true break-through in transducer architecture that performs so well across so many types of exams that you may never want to let it go,' the manufacturer reports.

Hitachi's next generation linear matrix transducer is the first and only commercially available in daily practice, Capacitive Micro-machined Ultrasound Transducer (CMUT), a technology so advanced that the inventors at the prestigious Stanford University in Palo Alto, California could take it no further than a prototype. After more than 12 years' work, the engineers at the Hitachi Ultrasound Research & Development Centre, in Tokyo, overcame the technical challenges to bring this innovative probe into daily practice.

No switch from high to low frequency sessions

'The most important thing about this new transducer is that clinicians no longer need to switch probes between high frequency and low frequency sessions,' said Hiroki Tanaka, one of the lead developers. 'Physicians can now use Hitachi's 4G CMUT for superficial examinations of the breast, for example, by applying a high frequency; then with this same probe, they can perform low frequency exams of the abdomen, liver or pancreas, for example. With this one probe, they can cover almost all applications in daily routine.'

Introduced at the 2017 European Congress of Radiology, the Hitachi 4G CMUT is actually the fourth generation of this technology, he pointed out.

Hitachi released the first-ever CMUT in 2009, which could generate excellent B-mode images using low power, but which limited its application primarily to breast exams.

The next generation offered an increased bandwidth, enabling higher two-dimensional quality with Tissue Harmonic Imaging and an increased sensitivity for Doppler and Colour Doppler to image blood flow.

The new linear matrix probe expands even further the bandwidth capacity to a range from 22 MHz down to 2 MHz, the low frequency needed to examine deeper structures in the human body.

All on a single wafer

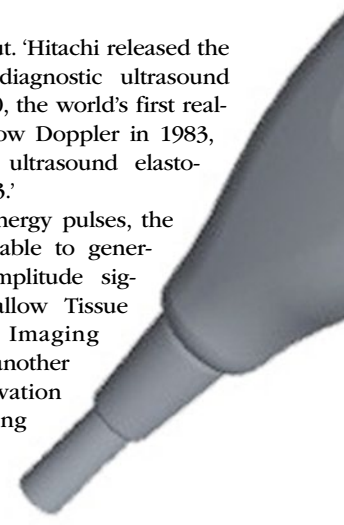
Open up any other ultrasound transducer and you will find hard ceramic crystals that have been hard-wired to generate and receive sound waves. Inside the CMUT you will find a soft membrane embedded with electrodes that vibrate to transmit an ultrasound signal.

The break-through with 4G CMUT is the micro-machined architecture on a silicon wafer. The membrane is less than three microns thick and behind this is a cavity of just 100 nanometres. The transducer array is constructed by combining a large number of these CMUT cells.

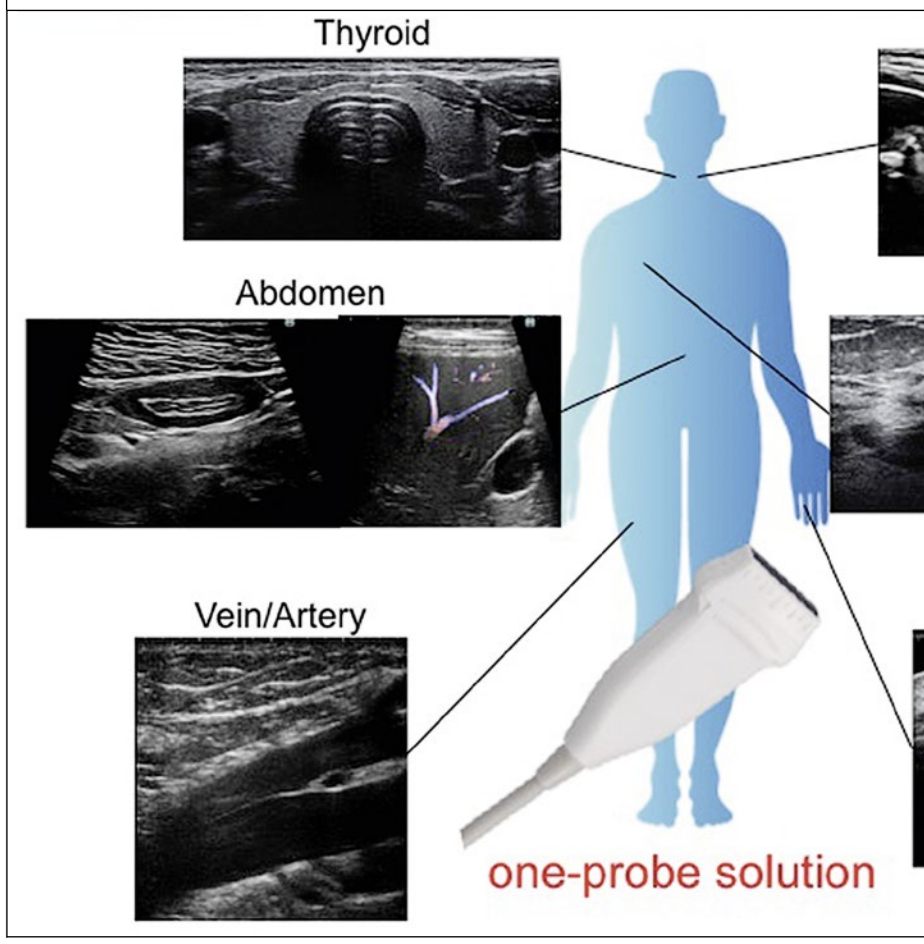
'The CMUT membrane is very close to the human body for its softness, so the ultrasound pulses smoothly from the probe and through the human body,' Tanaka explained. 'This architecture is more direct and precise with no deflection using very short pulses with no refraction wave. Because it transmits broadband, all frequencies are sending pure signals and nothing gets lost.'

Hitachi engineers also solved the problem of applying high power levels to the CMUT cell, an achievement that has created a stir in the engineering community and has further enhanced the reputation of Hitachi as the most innovative developer in the field of ultrasound, the company points out. 'Hitachi released the world's first diagnostic ultrasound system in 1960, the world's first real-time colour flow Doppler in 1983, and invented ultrasound elastography in 2003.'

With high-energy pulses, the 4G CMUT is able to generate higher amplitude signals, which allow Tissue Harmonic Imaging thanks to yet another Hitachi innovation for modulating the amplitude, the company adds. In addition, matrix array allows control of the short axis focus and to



One probe, yet the device can perform many examinations



ore comfortable

gery lists has improved too, as we work almost in parallel with the surgeon; while one patient is in theatre, we administer a block to the next person, reducing the impact of anaesthetic time and increasing throughput. In addition, we've trained our A&E colleagues to administer ultrasound-guided fascia iliaca blocks to trauma patients. This has really improved the quality of care, ensuring patients are comfortable during transfer between A&E and the X-ray department, and minimising the morphine dose required.

When ultrasound guidance first became mandatory for vascular access, we set up a training course for all doctors within the organisation who were placing central lines. Over time, as the use of ultrasound became commonplace, this knowledge began to be handed down informally, rather than through attendance at training courses. The risk with this approach is that messages get diluted, and so we prefer trainees to undergo more formalised training for this procedure, as they do for ultrasound-guided regional anaesthesia. It is important that they realise that they are looking at a computer-generated image and are aware of the potential for artefact formation, as well as understanding how this occurs. We also run basic level training courses for senior house surgeons across the region, plus more advanced courses that are open to clinicians from outside the area.

Ultrasound guidance is now an established procedure at the Salford Royal, and we have a considerable number of SonoSite systems shared across 20 theatres – including two X-Portes, an Edge, two M-Turbos, three S-Nerves, a MicroMaxx and three iLooks – which are used for both regional anaesthesia and vascular access. The systems are reliable and user friendly, and the customer service is good. The X-Portes have become particularly popular, not only for anaesthesia, but also for central line placement. People like the big screen and wipe-clean surface, and the training features are really good. If a trainee wants to refresh their knowledge of particular anatomical landmarks, they can simply watch the relevant video, which acts as a mini tutorial.

The big advantage of ultrasound guidance is the safety and reliability it offers, even when you are treating a patient with difficult vascular access; a large lumen line, for example, can be safely inserted using the Seldinger technique. Ultrasound makes a huge difference; it allows you to do things differently – and is saving lives.

Jim Corcoran is a consultant neuroanaesthetist and the clinical director of perioperative care at Salford Royal Hospitals NHS Trust, a trauma centre in the Manchester conurbation and the busiest neurosurgical centre in the UK.

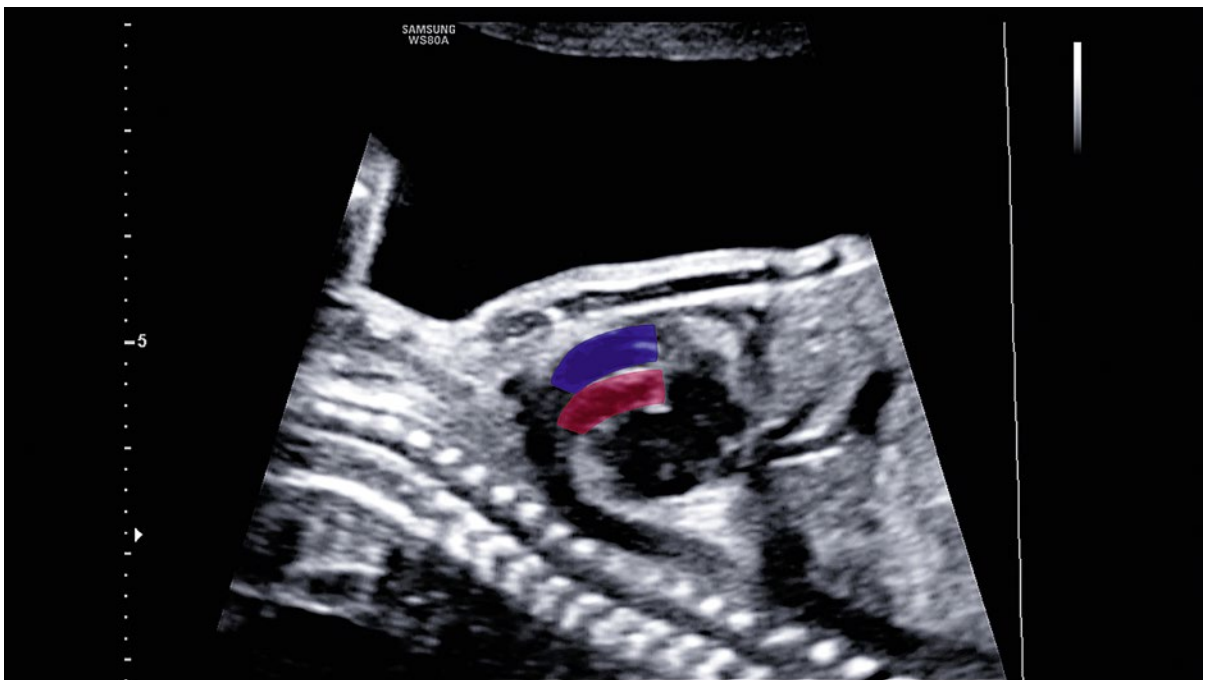
optimise the slice beam in any depth automatically to obtain the high image quality at wide range of depth.

The 4G CMUT is one of the leading features of the ARIETTA 850, the premium ultrasound platform also introduced at ECR 2017. Combined with eFocusing, a dynamic transmission and reception technology, and a 22-inch wide Organic Light Emitting Diode (OLED) monitor the ARIETTA 850 maximises the performance of wide bandwidth 4G CMUT and opens the door to the next stage in ultrasound.

1st trimester scan should check for congenital heart defects

All unborn babies need foetal echocardiography

Acknowledging the need for faster ultrasound automation, during our *European Hospital* interview Dr Alexander Weichert, gynaecologist and obstetrician at the Charité University Hospital Berlin, explained how automated procedures can assist in the early detection of cardiovascular disease and prenatal diagnostic testing, and why a detailed prenatal diagnosis can reduce mortality and morbidity.



With transposition of the great arteries (TGA), the aorta (blue) rises from the right ventricle; the pulmonary artery (red) from the left ventricle and the foetal echocardiogram shows the typical parallel connection

'Congenital heart defects are among the most common congenital defects, so they are of great importance in prenatal diagnostics,' Alexander Weichert pointed out. 'Unfortunately, they are often still not diagnosed.

'Under optimum conditions they can be diagnosed from the first trimester scan, i.e. between the 12th and 14th week of pregnancy. Most heart defects are diagnosed at the mid-pregnancy scan, i.e. between the 20th and 22nd week of pregnancy - but still not often enough.

'Only a minority of heart defects is diagnosed prenatally because not all pregnant women are systematically scanned by an echocardiographer. Only when risk factors, such as multiple pregnancy, growth delays, or other suspicious factors come into play these cases are referred to specialists. Specialist diagnosis or screening for cardiovascular pathology is therefore rarely carried out.

'This can be fatal because, unlike CT or MRI, ultrasound is a procedure that very much depends on the skills of the user. The ability to diagnose congenital heart defects takes years of practice. There are obviously guidelines for the visualisation of certain examination planes, but this in turn also requires intensive experience with ultrasound procedures. This is common in many countries.'

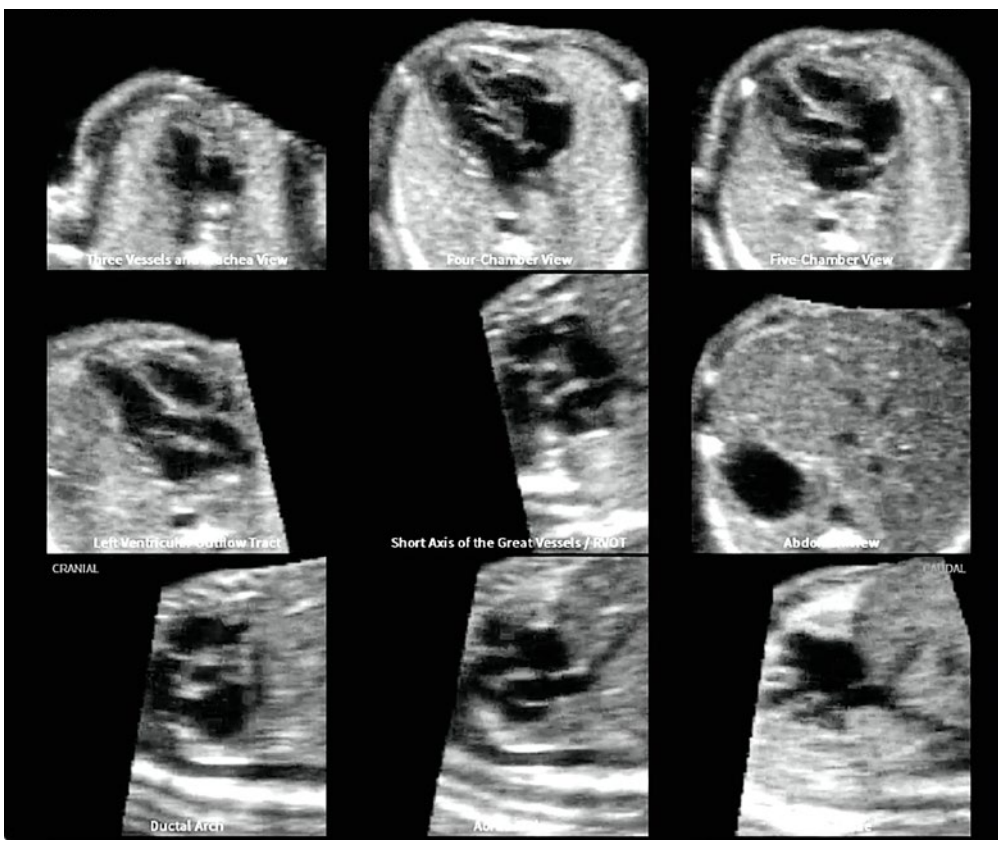
Prenatal intervention

'Some heart defects can already be treated prenatally. This includes aortic stenosis, which can be treated via cardiac catheterisation. Early diagnosis in itself – even without immediate treatment – has further, fundamental benefits, as confirmed by numerous studies: If congenital heart defects are diagnosed in time, this results not only in lower mortality and morbidity but also in less time spent on intensive care wards and improved surgery results. Early diagnosis facilitates optimum preparation, as congenital heart disease may require fast action after birth, especially for defects affecting the ductus arteriosus.

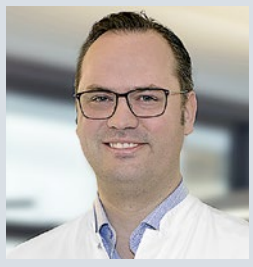
'Before birth, there are connections in the atrial septum (foramen ovale) and between the large blood vessels (ductus arteriosus), which form a parallel connection of the pulmonary and systemic circulation.

'Heart defects where the blood cannot flow directly to the lungs or the body, due to an obstruction, but with a detour via the ductus arteriosus, are known as patent ductus arteriosus.

'Before birth this is unproblematic because there is a connection between the two circulations. After birth, however, this connection, which is vital for children with patent ductus arteriosus, closes, leading to a life-threatening lack of oxygen and a race against time. If the heart defect is known in advance, the ductus arteriosus can be kept open through the administration of Prostaglandin E1. The medication keeps the parallel connection intact and buys the paediatric cardiologist or heart surgeon time for detailed surgical planning. A situation that may become life threatening can be significantly eased through early diagnosis.'



Nine examination planes are extracted from a volume data set of a foetal heart after marking seven reference points



Senior Consultant Obstetrician and Gynaecologist at the Charité University Hospital in Berlin, **Alexander Weichert MD** heads the Maternal-Foetal Medical Unit. His magna cum laude doctorate was gained at the Charité and he is a DEGUM level II certified sonographer. His specialties include prenatal diagnostics and therapy, special obstetrics, premature delivery and perinatal medicine. He is also a member of the German Societies of Ultrasound in Medicine (DEGUM), Perinatal Medicine (DGPM), Gynaecology and Obstetrics (DGGG), the Empress Auguste Victoria Society for preventive paediatrics (KAV) as well as the International Society of Ultrasound in Obstetrics and Gynaecology (ISUOG).

Which ultrasound procedures do you use for diagnoses?

'In the first instance, the common B-mode image and the "simple", two-dimensional ultrasound, then also colour or pulsed Doppler ultrasound. Further methods are not needed for precise diagnosis. However, for teaching and documentation, 3-D or 4-D technologies are of advantage.

'When it comes to patient contact, 3-D representation helps with our main objective, i.e. to build trust and to still expectant mothers' fears. 3-D- and 4-D methods are also important for cooperation with the paediatric cardiologist, as the prenatal examination planes do not correspond with those important for postnatal examinations. 3-D or 4-D diagnostic results can simplify the dialogue with the cardiologist and bridge the gap between diagnosis and therapy.

Automated procedures to improve ultrasound use

'There is currently a heated discussion around this under the key words "operator support". There are different approaches to automation, one of the most prominent being so-called foetal intelligent navigation echocardiography, or FINE technology. The procedure entails using a cardiac volume data set where seven central points are marked. The system then automatically generates nine scanning planes for diagnosis.

'This technology was published in 2013 under the direction of Dr Roberto Romero and Dr Lami Yeo from Detroit. The algorithm has the potential to improve the use of ultrasound – but only if the quality of the data set used to generate the scanning planes is sufficient.

'Therefore, I am advocating the development of technology that facilitates automatic quality controls, and which gives automatic feedback, whether certain requirements are being met even during the scan. Another desirable feature would be a type of autofocus that automatically centres and sharpens an image, just like a camera – but this is still pie in the sky. Until then, it will remain our heartfelt wish that all unborn babies will be given a routine foetal echocardiography as a preventive measure.'

Ultra-early detect foet

Study shows a simplified examination can b tions during the first trimester of pregnancy

In just two weeks Dr Edwin Quarello, from St. Joseph Hospital in Marseille, had the answer to a clinical question he had been asking for years: Is it possible to check for major congenital heart defects (CHD) across the general population of pregnant women before the second trimester?

Over the past 15 years foetal echocardiography exams have been increasingly used to detect CHD in high-risk populations, yet a 2004 study published in Prenatal Diagnosis showed that most cases of CHDs would occur in low-risk populations.

Heart defects are a leading cause of death during the first year of life, touching five to nine newborns in the general population, and nearly every case of CHD is already established in the foetus by the first trimester.

Quarello has been preaching the benefits of early detection in the first trimester, and teaching colleagues in the south of France how to perform what he calls the basic exam for the past 10 years.

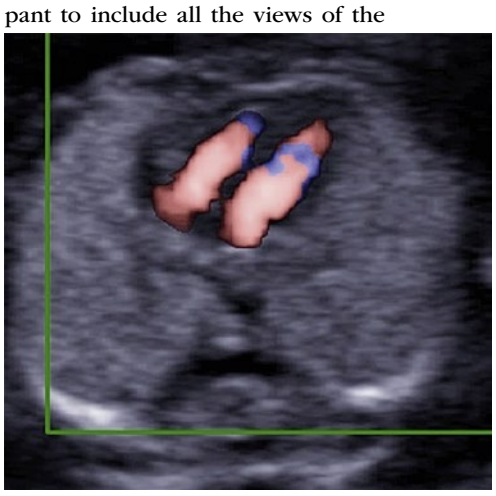
Last year he decided to use a novel methodology called a 'flash study', supported by the French College of Foetal Ultrasound (CFEF), to find out if the basic protocol could be competently performed by someone with basic ultrasound skills.

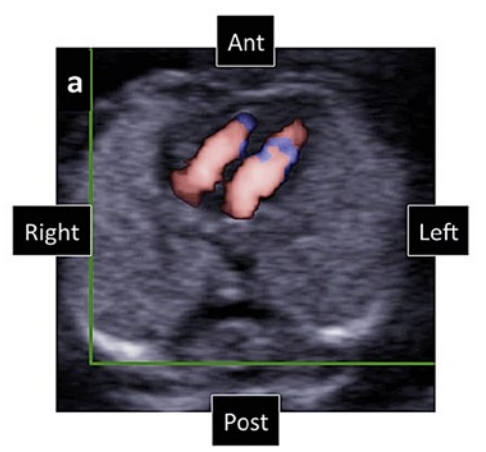
That French twist in clinical studies was introduced at the 2010 meeting of CFEF by Dr Laurent Salomon, who participated in this study and is a co-author of the resulting paper.

The focus for a flash study must be narrowed to a single question, Quarello explained, and it must be conducted in a very short period, in this case just two weeks.

More than 150 physicians and midwives responded to his invitation to participate in the study.

'What we asked was whether it would be possible for the participant to include all the views of the





Five to nine newborns suffer cardiac problems

y ultrasound can tal cardiac defects

pe performed routinely on low-risk popula-y, John Brosky reports

heart that we wanted to use for the study without modifying their time or methods during a routine first-trimester ultrasound examination.' In one word, the answer is yes.

In a paper published in February, 2017 in Ultrasound in Obstetrics & Gynaecology, Quarello, et al. wrote: 'This is the first such study of the feasibility of a first-trimester basic heart examination; the study was multicentric as opposed to previous studies in individual centres; the majority of observers were not echocardiography experts; and we present new criteria for assuring and assessing the quality of foetal echocardiography when obtaining 4CV (four-chamber view) and 3VT (three vessels and trachea) view cross-sections through the use of colour and/or power Doppler modes.'

'In the end only 60 participants completely fulfilled the criteria,' Quarello said. Twelve were midwives, 48 were physicians.

Asked if this meant that roughly one in three willing participants was actually qualified to perform the basic exam he designed, Quarello sighed, responding: 'Many cases were excluded for reasons completely outside the technical skills of the physician or midwife performing the exam. The truth is that, in addition to the images, participants were required to provide patient information, such as last name, first name, date of birth, and so on. Where this information was not complete, the case could not be included in the study. Some participants simply did not know how to send the images electronically.'

The entire study was conducted by email, he said.

Despite this limitation inherent in a flash study, the 60 participants who met the quality standards performed an average of 10 exams for a total of 597 cases of first-trimester ultrasound examinations screening for CHD.

The successfully acquired 4CV and 3VT views were assessed as normal for 435 cases, or 73 percent, thereby assuring parents. The remaining 30 percent of cases may merit a referral to a specialist.

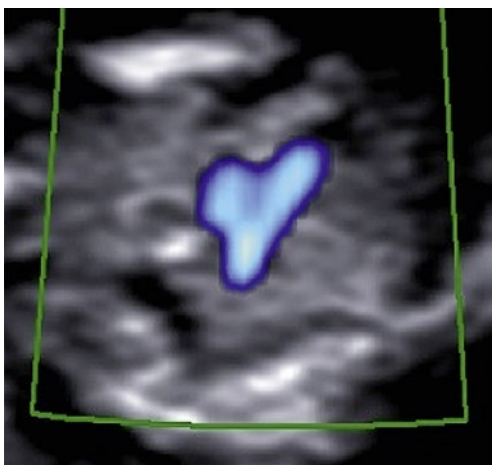
The authors note that some of the major CHDs detected would be amenable to skilled palliative surgery, while major defects, are associated with less successful surgical repair and termination of pregnancy may be an appropriate form of management.

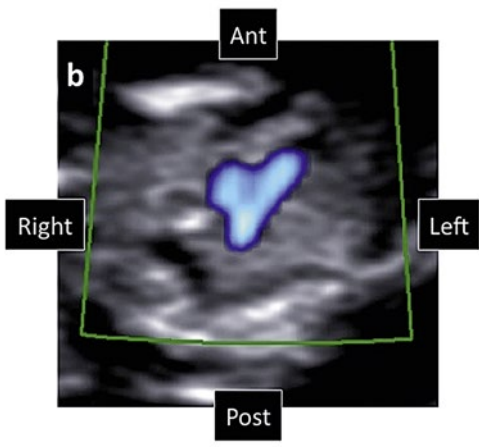
'Data suggest that psychological recovery after termination of pregnancy for foetal malformation is better the earlier the diagnosis is made,' they wrote, or as Quarello explained, before the mother begins to feel the child moving and develops stronger attachment.

'The reason we are encouraging this exam during the first trimester is not to say to the world that we are able to see everything, but to show that we are able to screen, potentially to identify a major problem, which is different,' he explained. 'This study demonstrates the basic foetal heart exam can be performed without a high level of skills, and this is a major advance.'

Edwin Quarello MD is an obstetrician specialized in fetal medicine at the Institute for Reproductive Medicine at the St. Joseph Hospital in Marseille, France where he leads the service for obstetrical echography and prenatal diagnostics. He is a former clinical fellow in fetal cardiology at the Royal Brampton Hospital and St. Georges Hospital in London, UK.

A basic heart exam in the first trimester using colour Doppler and/or directional power Doppler from the four chamber view as well as the three vessels and trachea view





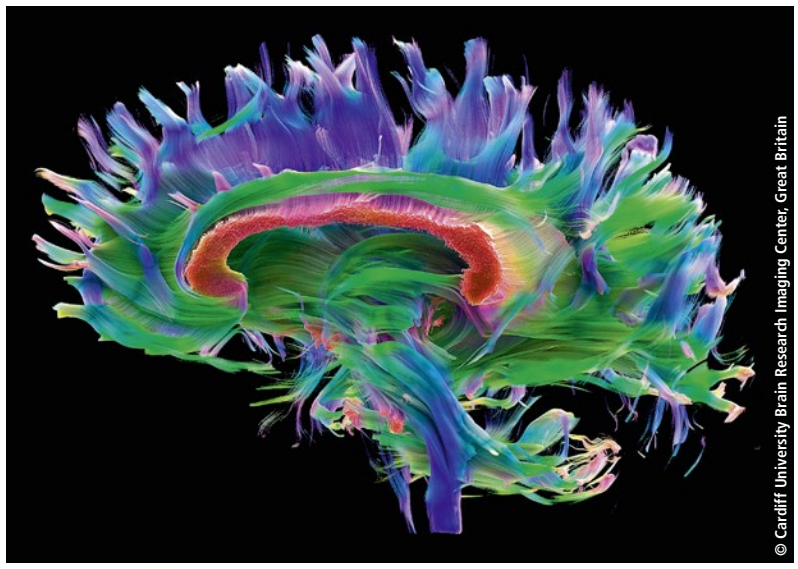
Cinematic Rendering undergoes tests for surgical procedures

3-D visualisation is like 'body cinema'

A physician has basically two possibilities to look inside a body: putting a scalpel to the patient's skin or using an imaging device. Both options have advantages and disadvantages. Now, Siemens Healthineers has combined the advantages of both methods and developed Cinematic Rendering, a new 3-D visualisation approach. The name already points to the roots of the technique – the cinema. But it does much more than providing impressive images.

Report: Wolfgang Behrends

The human body is a marvel, the anatomy highly complex. 'This complexity is difficult to grasp, particularly in the operating room,' says surgeon Dr Christian Krautz, who is heading the current clinical evaluation of Cinematic Rendering for surgery purposes at Erlangen University Hospital in Germany. The photo-like 3-D display of conventional DICOM images offered by the new procedure allows quick orientation inside the body. 'The technique makes it much easier for us to get an overview of individual anatomy,' Krautz explains. And, Professor Robert Grützmann, Director of the Surgery Department, adds: 'That's like body cinema. Even seasoned surgeons are wowed – it's a real help for our brains.'

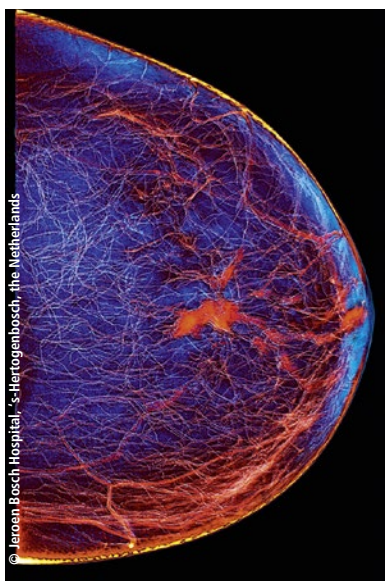


Fibre bundles of the brain – Cinematic Rendering based on data gleaned from magnetic resonance imaging.

Better overview in difficult situations

But how do spectacular images contribute to positive surgical outcomes? 'Take liver surgery,' suggests Christoph Löhr, Senior Manager for Strategy at Siemens Healthineers. 'The liver is a highly perfused organ surrounded by a thick layer of fatty tissue. Interlinked and adjacent vessels are visible neither with the naked eye nor on images. Even experienced surgeons have to use the combination of years of experience and haptics: they feel the vessels with their hands.' But things are easily overlooked – or rather "overfelt" – with potentially fatal consequences for the patient. Thus, 3-D visualisation of the layout is a huge help. 'This is exactly what Cinematic Rendering does per mouse click,' Löhr explains.

One of the main design ideas was to keep the operating concept of the software minimalistic: filter functions can show and hide bones, vessels and tissue. This provides images that immediately show clinical issues.



View of the breast and breast tissue; the red spot at the centre is a tumour – Cinematic Rendering based on tomosynthesis dataical

In the clinical study, cases are examined retrospectively to test the new procedure. Löhr: 'Surgeons see 2-D DICOM images as well as Cinematic Rendering images and are asked how they would decide based on these two types of images. We are particularly interested in complex cases such as pancreas or liver. These are organs where we expect the new technology to offer the greatest value-add and more security.'

The developers are confident that there are many more areas where Cinematic Rendering will prove its mettle. 'We see enormous potential in teaching, in patient communication and in forensics,' explains Dr Klaus Engel, Principal Key Expert at Siemens Healthineers and inventor of Cinematic Rendering. 'Moreover, tumour boards will benefit from the new technology because the images are easier to interpret. This will lead to a democratisation of the boards, faster agreement and hopefully to better decisions for the patients,' Grützmann believes.

Sophisticated algorithms for real-life applications

The hyper-realistic computer-generated images often resemble objects in the 'Body worlds' exhibitions. They are based on a sophisticated algorithm that creates spectacular effects, very much like in a Hollywood blockbuster: 'Unlike previous 3-D imaging procedures, Cinematic Rendering is based on physics,' Engel points out.

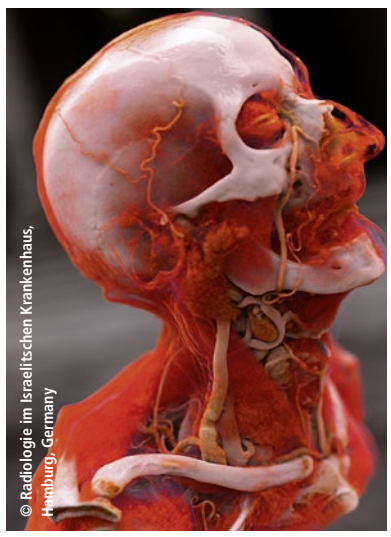
'While previously raycasting was used, which treats light rays as straight lines, the new technology includes a number of much more complex factors such as reflection and scatter.

'This results in 3-D images in cinematic quality but more importantly with added clinical value. 'A crucial feature is realistic shading,' the inventor adds. 'The human eye is trained from day one to recognise minute differences in shading and deduct the spatial location of an object. A shadow, for example, can indicate the depth of a given structure.

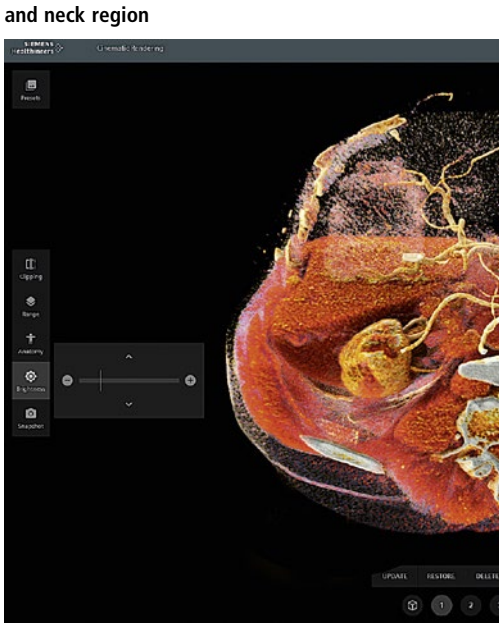
'Until today, we did not have this kind of information in 3-D imaging, which made the evaluation of spatial relationships, such as overlappings, very difficult. The new method offers a more sculptural approach. We consider surgery to be an important field of application where this innovation will be highly useful.' While Cinematic Rendering is technologically extremely sophisticated, it is versatile in its potential application. 'Today, PCs with the necessary computing power are easily available; the same holds true for imaging modalities, such as CT, MRI, PET and ultrasound. The system is DICOM-compatible, particular standards are not required,' Engel underlines.

Augmented reality – coming soon to your local operating theatre!

Currently Cinematic Rendering is under development for surgery application. 'In the prototype study we focused on therapy planning,' says Dr Stefan Assmann, Director of Adjacent Fields at Siemens Healthineers. 'The surgeons' feedback indicates that Cinematic Rendering may help to save time.'



Musculoskeletal structures in the head and neck region



The realistic depiction of volume datasets could make addition for surgical departments.

A chance to choose a top tutor for a surgical skill

Gaining the greatest practica

A French start-up eases international peer-to-peer teaching in TAVI, PRP or S-ICD and other leading medical procedures by taking physicians directly in the operating suites, Mélisande Rouger reports.

Mentors play a tremendous role in every profession but perhaps nowhere else as in medicine. As technology advances and procedures multiply at the speed of light, physicians increasingly need tutors to deliver optimal care. What better place to learn than with experts in their own environment?

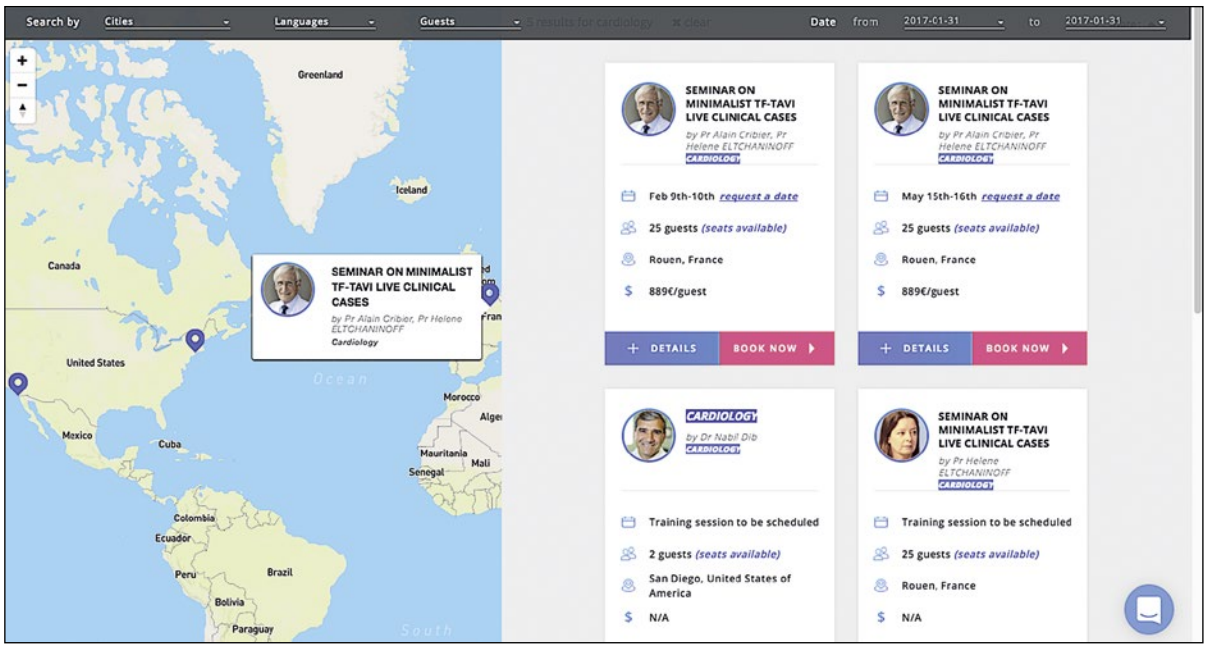
Bordeaux-based start-up Invivox is taking on the challenge to bring peer-to-peer teaching onto the global level, by enabling physicians to train with experts directly in surgical suites. 'Our goal is to become the Airbnb or Uber of medical training, by enabling physicians to find and book training opportunities with the best experts in their field,' explained Julien Delpech, CEO of Invivox.

Training slots in surgery, cardiology, urology and gynaecology are available on the platform, and the company plans to have every specialty on-board shortly. Invivox offers insight into medical practice by enabling participants to book entire days with experts while they are performing the procedures they have mastered on patients.

Experts are chosen by a scientific committee and can then sell training slots directly on the Invivox website. Typically, specialists invite two to three peers to spend a day with them, during which they will deal with both clinically and technically pertinent cases.

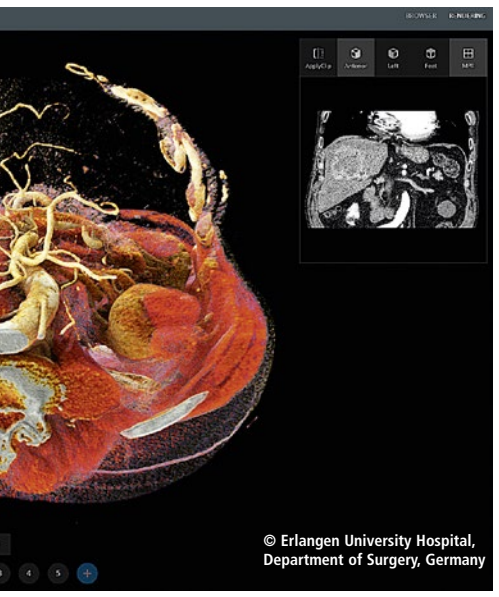
Personalised training proves invaluable

The solution answers a long time demand from physicians to receive personalised training in procedures that are proving indispensable in their field, according to Delpech: 'Whereas meetings, conferences and workshops are excellent for networking, they only partially meet physicians' needs for training in particular techniques.' Having worked in the medical field for over 15 years, he believes this ability to connect physicians to living legends in their field is the added value of the tool. For instance, the company attracted world famous cardiologist



Klaus Engel PhD invented Cinematic Rendering technology. Since 2009, the computer scientist has been Principal Key Expert at Siemens Healthineers. Specialising in visualisation research, prototyping and software development, he spent several years developing and fine-tuning Cinematic Rendering's algorithms.

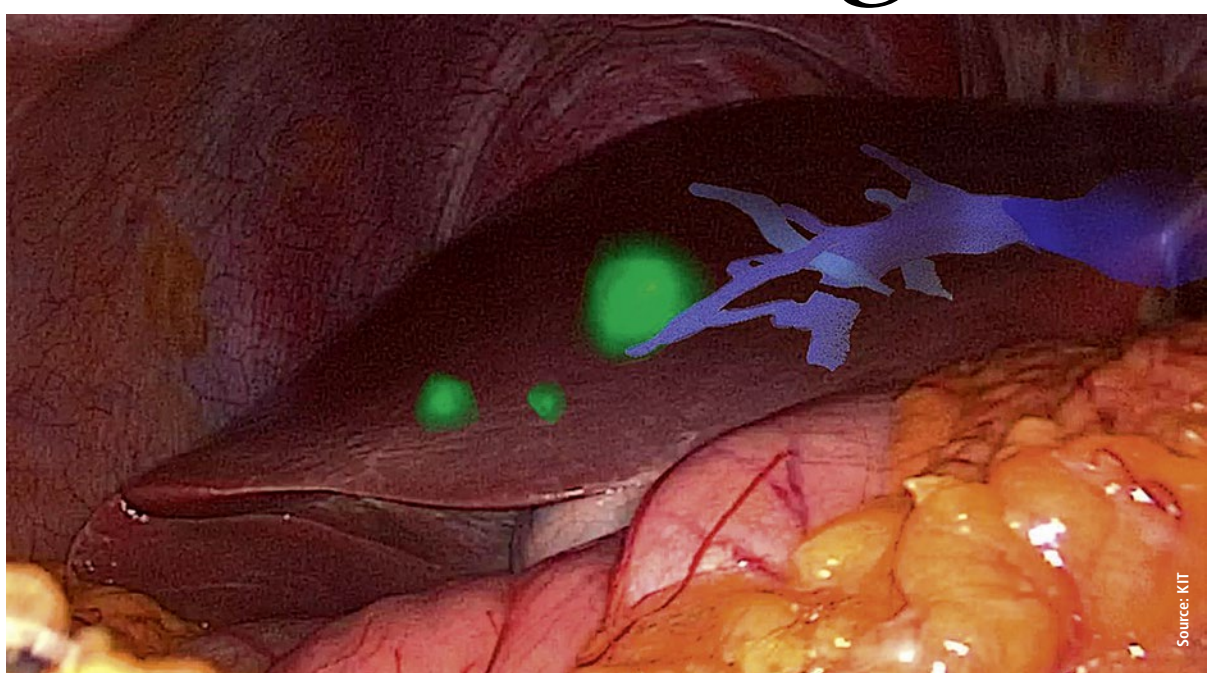
Grützmann agrees that the new method has enormous potential: 'I'm sure many possible applications will surface once the method is being used. Maybe one day we will even be able to show the images in augmented reality during an intervention – with the surgeon wearing special glasses.' Engel is equally enthusiastic. 'Imagine you have pre-op images which you can project onto the patient during the operation. That means you can look inside the patient before the first cut. This would be very useful above all in minimally invasive interventions.'



Cinematic Rendering a highly valuable

Computer scientists seek intelligent surgical assistance systems

Real time analysis for cancer surgeons



Smart aid in the operating theatre: 3-D images of the tumour (green) and the vessel structure (blue) are inserted into the endoscopy image of the liver

Interview: Katrin Schreiter

Computer scientist Stefanie Speidel, who became a Professor for Translational Surgical Oncology at the National Centre for Tumour Diseases, in Dresden in Germany this April, researches intelligent assistance systems for the operating theatre. During our *European Hospital* interview the professor spoke of intelligent assistance systems currently in development, robotic assistance systems already in use in medicine and software for smart glasses.

'Robots in the operating theatre, for instance the Da-Vinci-System, are good mechanical aids,' Speidel pointed out. 'But we want to make additional help available with our specialist software. This should improve the surgeon's work even further, particularly for minimally invasive interventions. The software delivers images during surgery that display additional information, such as details about the exact location of a tumour. This is particularly important when the surgeon operates on soft tissue in the abdomen, for example. Breathing, heartbeat, or the use of mechanical instruments, continuously change the position and shape of tissue and organs. The software helps to predict this movement and adapts the surgical intervention accordingly – and in real-time! This goes way beyond the information doctors receive prior to a CT scan, for instance.'

How the software works

'We combine image and sensor data obtained prior to and during surgery with biomechanical models and develop new programmes that can instantaneously calculate positional changes with this information. This is especially helpful for cancer surgery because interventions can be carried out more precisely and tumours can be completely removed with more certainty – without removing too much healthy tissue and without injury to important blood vessels, as doctors also receive relevant information during surgery.

A virtual reality solution

We are also developing special software for smart glasses to help the surgeon to obtain a three-dimensional model of the operating field prior to surgery. The smart glasses are used for planning prior to surgery. So far, we have had very positive experiences; surgeons have been very accepting of the system.'

Might a doctor one day be assisting a robot or the software?

'No. We are basically trying to provide assistance during surgery by processing complex amounts of data to make the right information available at the right point in time – but the ultimate medical decisions will always be made by humans.'

Is a leading female computer scientist a bit rare in Germany – and was the ascent rocky?

'I can't actually say that. I've always found myself in supportive environments, and walked straight through all the doors that opened for me. But yes, there are not enough role models in Germany. Comparing it to the situation in Spain, you will notice a big difference as the number of women studying information technology there is much larger, but there seems to be more hesitance around this topic here.' 'Generally, women should be more confident, give things a try and not question themselves even beforehand… We can certainly learn something from men here!'

Foto: NCT Dresden/André Wirsig

Stefanie Speidel studied at the technical University of Karlsruhe (in her home town) in Germany and at the Royal Institute of Technology, Stockholm, Sweden. Post-graduate research followed at Heidelberg University, Germany. Since 2012, she has also run a junior research group on computer-assisted surgery at the Karlsruhe Institute of Technology (KIT). Among a number of scientific honours she gained the Technology Award of the European Association for Endoscopic Surgery (2007), the Maria Gräfin von Linden Prize (2011) and the Margarete-von-Wrangell-Fellowship (2011). Speidel also received two awards for outstanding teaching. This April she became Professor for Translational Surgical Oncology at the National Centre for Tumour Diseases (NCT) in Dresden, which was set up by the German Cancer Research Centre (DKFZ), the Faculty of Medicine Carl Gustav Carus of the Technical University Dresden, the University Hospital Carl Gustav Carus Dresden and the Helmholtz Centre Dresden-Rossendorf (HZDR).

al guidance

Alain Cribier, who invented trans-arterial venous implant (TAVI) over a decade ago. 'Physicians say it's an opportunity they couldn't even have dreamed of. Cribier is TAVI's rock star, people wouldn't even think of sending him a mail, but there he is, available on our website,' said Delpech, who is currently opening the company's US office in New York City.

The formula has attracted an increasing number of physicians and investors ever since its launch in 2015. The platform features about 900 registered users and 105 training opportunities, and attracted €1.2M from various actors in and outside healthcare in March 2016.

Accepting a price to pay for mentoring

Guy Magalon, a renowned plastic surgeon from Marseille, France, has become a regular trainer. He has offered four trainings in platelet-rich plasma (PRP), a treatment he has mastered for scleroderma, an orphan disease. He echoed that the benefit of the tool lies in creating links between physicians of different horizons and levels. 'Invivox connects people, who may never have met otherwise,' he said.

He also thinks specialists from different disciplines are bound to share training in innovative techniques, such as PRP, which sits at the crossroad of biology and surgery.

But physicians must learn to use this brand new service, which is changing the concept of mentoring, except for the proximity to one's tutor.

'There is nothing like seeing the gestures live to learn,' he emphasised. 'Invivox is introducing the concept of money into mentoring, so people have to get used to it.'

The average cost of a training slot is €1,100 per participant and each can gain Continuing Medical Education (CME) credits as well as a diploma declaring he/she has received expert training.

The company is now establishing the service and aims to receive recognition by the competent institutions and scientific societies. In January 2016, it secured partnership with the Italian Society of Reconstructive Surgery and expects to augment its offer in this and other specialties.

After spending years in operating suites where he trained surgeons to use evolving medical devices, **Julien Delpech** co-founded and became CEO of Invivox, which specialises in peer to peer teaching. His 15 years' experience in sales and marketing operations for major international medical leaders (Allergan, Ipsen) in France, Latin America, the USA and Eastern Europe, have proved a considerable asset.

Facing spectacular outcomes or dramatic side effects?

Understanding and utilising immuno-oncology

Report: Anja Behringer

Every cancer is different and every patient is different. This insight gained in personalised medicine prompted oncology researchers to focus more on the individual patient's immune system. It is particularly the immune system's ability to destroy cancer cells that raised hope.

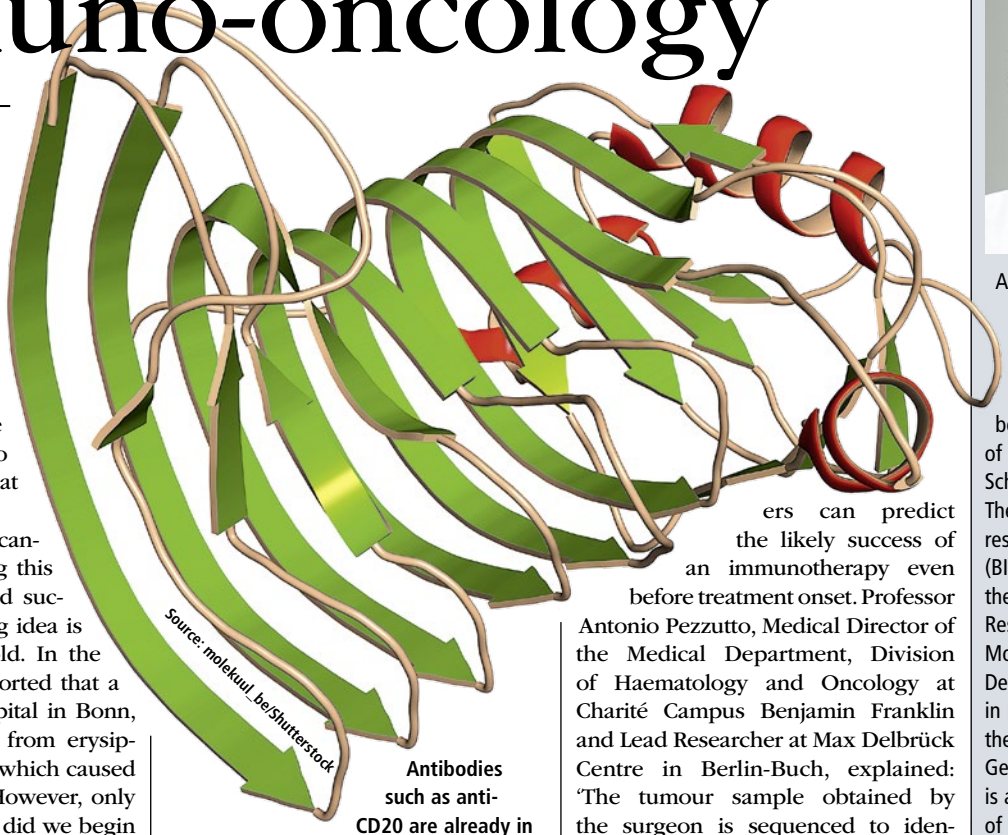
Today, a number of cancer therapies harnessing this ability are being applied successfully. The underlying idea is more than 150 years old. In the 19th century it was reported that a cancer patient in a hospital in Bonn, Germany, had suffered from erysipelas, an acute infection, which caused the tumour to shrink. However, only in the past two decades did we begin to better understand the complex interaction between cancer cells and the immune system, knowledge that allowed us to venture into uncharted treatment terrain.

Although there have been impressive successes, in particular with malignant melanoma and advanced lung cancer, scientists continue to face major challenges. A close cooperation of researchers, researching physicians and clinicians is needed to unlock the cancer cells' secrets.

Generally speaking there are two types of immune responses: the innate immune system responds in a generic way to all pathogens and wards off most infections. By contrast, the acquired (or adaptive) immune system eliminates specific pathogens with the help of B cells and T cells 'despatched' as soon as certain structures of pathogens and cells, so-called antigens, are detected. The acquired immune system stores information on any initial response to an antigen in a memory, i.e. it recognises this antigen later and responds accordingly.

The immune system recognises cancer cells by the so-called tumour-associated antigens (TAA) on their surface. Many tumour cells, however, have developed strategies to mask their malignant identity, for example by not presenting antigens. Alternatively, the tumour cells interact with the t-cells via so-called immune checkpoints. While these molecules normally prevent an over-reaction of the immune system, tumour cells use this mechanism to avoid their own destruction.

This is where immune checkpoint inhibitors come in: drugs that undo the cancer-caused blockage and stimulate the immune system to destroy tumour cells. In 2001, ipilimumab, the first immune checkpoint inhibitor was approved to treat advanced melanoma. A second drug, nivolumab, shown in clinical studies to significantly prolong survival, received approval in 2015 to treat advanced lung cancer. Renal cell carcinoma, Hodgkin lymphoma and carcinoma of the bladder have been treated successfully with checkpoint inhibitors and further immuno-oncological drugs are likely to be available in the future.



Source: molekuul_be/Shutterstock

Antibodies such as anti-CD20 are already in successful clinical use.

Unmasking strategies

Another promising immuno-oncological approach is the adoptive T cell therapy (ACT): patient T cells are removed, transfected ex vivo with tumour-specific T cell receptors and re-infused into the patient to recognise and destroy tumour cells. In therapies involving chimeric antigen receptors (CARs) T cells are removed from a patient, modified with a CAR specific to the patient's particular cancer and re-inserted. The modified T cells recognise corresponding antigens, such as CD19, which is present in most B cell melanoma. They dock onto the antigen and destroy the tumour cells.

The German Cancer Society reports successful application of this method: In several therapy studies on anti-CD19-CAR T cell transfer, patients with pre-B-cell acute leukaemia (ALL), chronic lymphocytic leukaemia (CLL) or B-cell lymphoma showed remission rates of 30 to 90 percent.

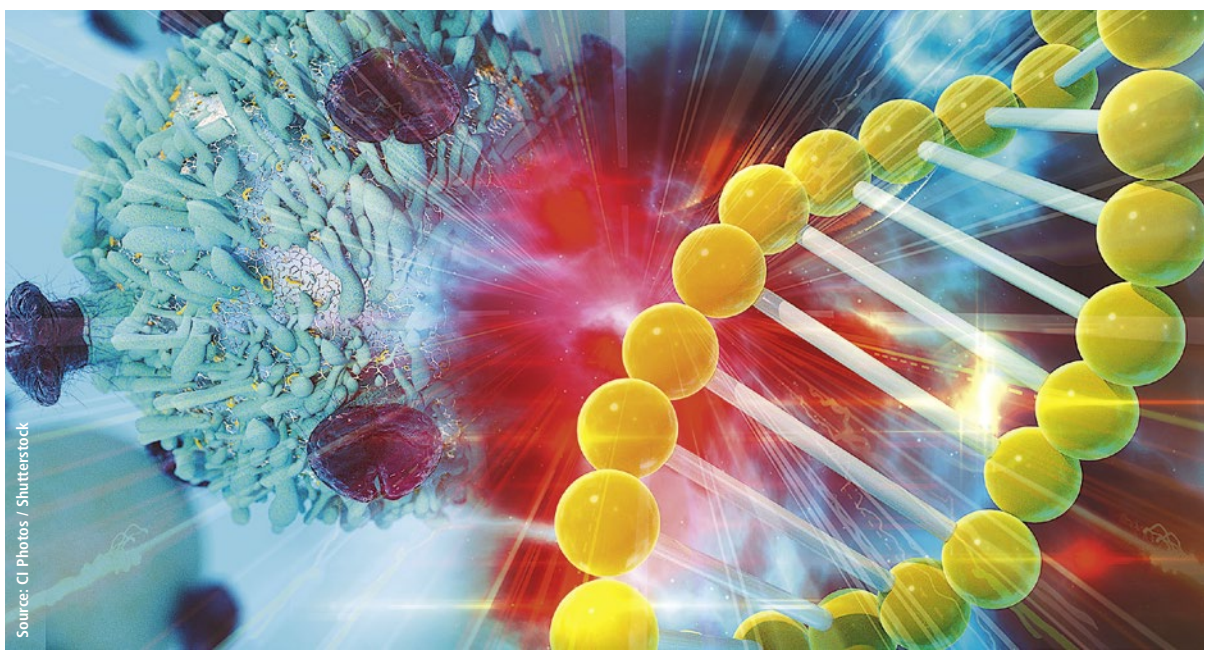
Bespoke therapies

Cancer researchers aim to fine-tune these therapies ever more precisely to the individual disease pattern. With the help of molecular high-throughput analysis they can indeed identify target structures on the cancer cells for the individual tailor-made immunotherapies. Even more: biomarkers can predict the likely success of an immunotherapy even before treatment onset. Professor Antonio Pezzutto, Medical Director of the Medical Department, Division of Haematology and Oncology at Charité Campus Benjamin Franklin and Lead Researcher at Max Delbrück Centre in Berlin-Buch, explained: 'The tumour sample obtained by the surgeon is sequenced to identify all mutations in the tumour cells. Only mutations that are essential for tumour cell growth are taken into consideration for a personalised immunotherapy. If we have, let's say 2,000 mutations in a tumour cell, it may well be that only 100 of those modify the structure of important proteins. The mutated protein pieces have to reach the cell surface for the immune cells to be able to recognise and attack them. In the end, maybe only a handful of potential targets materialise.' In a large project carried out by the Berlin Institute of Health (BIH) along with Charité and the Max Delbrück Centre, the potential of such individualised cancer therapies is being explored and the foundation for initial clinical studies is being laid.

The team encompasses computer scientists, oncologists and internal medicine specialists; biologists create specific immuno-cells, gene transfer specialists are on board as well as specialised 'mice immunologists' whose task it will be to validate the efficacy of the therapies in the animal model. It takes months of intensive research until tumour cell sequencing of a single tumour sample generates candidate cells. The costs of new immunotherapy approaches using the so-called adoptive T cell transfer can significantly exceed €100,000 per case. However, as Dr Pezzutto points out, tumour sequencing generates information that is relevant for conventional therapies. Since only very few patients benefit from the many new and expensive therapies that were developed over the past few years, the process to identify candidate patients is being constantly improved. 'If only 20% of the patients benefit from a therapy – a therapy that might be associated with dangerous side effects caused by unspecific activation of the immune system – it is crucial that we try to precisely identify the patients who might benefit. If we don't do that, we expose 80% to an unnecessary risk,' Pezzutto explained.

European Hospital asked Dr Lothar Kanz, haematologist and oncologist, Medical Director and tenured professor at University Hospital Tübingen, which of the immuno-therapies currently being applied offer the highest patient benefit. 'Monoclonal antibodies', he immediately responded, 'since several antibodies, such as anti-CD20, are already in successful clinical use. Moreover, there are enhancements, such as Fc optimisation, that offer increased biological effect.' In addition to checkpoint inhibitors, Kanz also uses monoclonal antibodies with attached toxins (antibody-drug conjugates/immunotoxins), bispecific antibodies, for example against advanced lymphocytic leukaemia. He will soon add CART cells, patient lymphocytes that are genetically modified in the lab, to his therapy portfolio.

T cells are modified specifically to the patient's particular cancer



Source: CI Photos / Shutterstock

A medicine graduate from the University of Padua/Italy in 1978 and in 1991, three years later **Antonio Pezzutto** was appointed Director at the Charité, Campus Benjamin Franklin and, in 2001, became Deputy Director of the Department of Haematology-Oncology, Charité Medical School at Campus Virchow Hospital, Berlin. The professor also carries out translational research at the Berlin Institute for Health (BIH) in cooperation with Charité and the Max Delbrück Centre for Clinical Research. In 1997 he initiated and led the Molecular Immunotherapy Group at Max Delbrück Centre for Molecular Medicine in Berlin-Buch. He has been member of the German Medical Associations' Somatic Gene Therapy Commission since 2000 and is also a member of the American Society of Haematology, the German Society of Haematology/Oncology and the German Society of Rheumatology.

A medical graduate from Freiburg University Hospital in Germany in 1995 **Lothar Kanz MD** became Medical Director and tenured professor at Eberhard Karl University, Tübingen, Department of Oncology, Haematology, Immunology, Rheumatology and Pulmonology at the Medial Clinic and Policlinic. In 1996, he received the European Research Award for Haematology. Since that year he has been Lead Scientist of the bi-annual 'International Stem Cell Conferences'. His research focus is haematopoiesis, immunotherapy and clinical oncology (Phase I/II studies on solid tumours; multiple myeloma). Kanz is member of the International Society for Experimental Haematology (ISEH), the American Societies of Haematology (ASH) and Clinical Oncology (ASCO) as well as the European Society of Blood and Marrow Transplantation (EBMT).

Side effects: dramatic autoimmune responses

While most side effects associated with immunotherapies are considered acceptable in view of the severity of the diseases, some dramatic autoimmune responses were reported, such as the rejection of the patient's own heart, and further rare adverse reactions to checkpoint inhibitors have to be expected.

It is crucial to strike a balance between stimulating and inhibiting the immune system in order to avoid the negative effects of an over-active immune system. Infections of the hypophysis, eyes, lungs, kidneys liver, colon or skin can occur and the therapy has to be discontinued.

While study results on tailor-made immunotherapies are promising, the practical application of these therapies is a long way away. The major translational obstacle, according to Kanz, is compliance with the strict regulations regarding Good Manufacturing Practice (GMP), i.e. the production of cells for cell therapies. In addition, he points out, the approval procedure for Investigator-Initiated Studies (IITs) is complex, long and expensive.

Immunotherapy going forward

Cancer researchers not only aim to develop new drugs, they also try to find out whether combinations of immunotherapies and conventional therapies, such as radiation or chemotherapy, or the combination of two immunotherapies, yield long-term successful outcomes. However, they have to acquire an in-depth understanding of the complex mechanisms of the immune system before they can develop strategies to reliably and effectively fight cancer with the body's own defence system.

The most recent research results on these issues will be presented at the annual congress of the German, Austrian and Swiss Societies for Haematology and Medical Oncology (Stuttgart. 29 September to 3 October).

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CARDIOLOGY 2017

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The ESC Congress 2017

With 4,500 accepted abstracts, 600 sessions and 30,000 expected attendees, ESC Congress 2017 is undoubtedly the world's largest cardiovascular event. European Hospital correspondent Mélisande Rouger asked Dr Stephan Achenbach, Congress Program Committee Chairperson, for an overview of issues and events unfolding in Barcelona from August 26-30

During the Congress, explained Stephan Achenbach, the ESC issues guidelines on how to manage patients with cardiovascular disease. 'In 2017 the guidelines focus on how to treat ST myocardial infarction, valve disease, peripheral artery disease and dual antiplatelet therapy, which is very important in coronary intervention.

'The Hot Lines presentations are late clinical trials; we have very promising publications, especially in the field of prevention – both primary and secondary. 'We also commemorate the anniversary of percutaneous coronary intervention. Forty years ago, Andreas Grüntzig performed the first balloon angioplasty of coronary artery stenosis.

'This year, we'll learn a lot that's new about the connection between heart disease and inflammation, considering the huge amount of abstracts received on the topic.

'Many of our sessions are joint sessions with partners, for instance sister associations such as the American College of Cardiology, the American Heart Association, the Japanese circulatory society, and the Indian and Chinese cardiac societies. 'We will also have sessions with subspecialty societies, including European Society of Hypertension and the European Society of CardioVascular Surgery, but also with genetics cardiology, pediatric cardiology, etc.

'Last, but not least, we will have very interesting sessions with the New England Journal of Medicine, JAG and the Lancet.

'This is a new addition because digital health is really becoming important in cardiology. We're cooperating with Mobile World Capital Barcelona, a tremendously large congress on mobile technologies. We will have interactive lecturers sharing their experience of mobile technology in cardiology.'

'Our challenges arise from the opportunities. Today we have many more options to treat and prevent cardiovascular disease, but they are expensive and we need to find resources and to direct those resources to patients who really need it. I think that's the challenge. As our opportunities become more complex we have to ensure that they remain economically viable. European research focuses on many aspects, but mainly on the development of percutaneous valve disease

treatment, really advancing percutaneous catheter-based treatment of aortic stenosis and percutaneous treatment of other valve disease. Europe really has a leading role there.

'Personally I am also involved with imaging, in the context of these new valve treatments, to prepare and guide the procedure and to decide which strategy to use in which patient.

'Imaging is tremendously important to fix heart disease. There's a growing interest among cardiologists to use imaging and high-end imaging using computed tomography or magnetic resonance."

'Europe has this very wide spectrum of high and low-income countries, so the field is very heterogeneous. The ESC has to cater to all these countries. 'In terms of trends, Europeans are traditionally early adopters of new technologies, treatments and diagnostic methods. They need to make these strategies economically viable.'

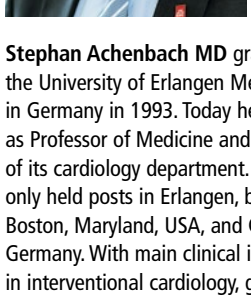
'Issues of data sharing and privacy, and selecting meaningful data are very important in cardiology as in any other field.

'The ESC has a working group on e-cardiology and the congress will feature sessions on e-cardiology and big data. Data is both a major opportunity and a problem.'

'The most important and promising indication for wearable devices use is screening for atrial fibrillation because it predisposes to stroke. Some research at the ESC will focus on that aspect.

'If you can find fibrillation early, you can prevent stroke, so this is a major opportunity for wearable technology, and it has not been looked at extensively yet. In the future there will be other indications, and there will be indications for cardiovascular risk factors such as diabetes and hypertension.

'There's also a new generation of devices that are implanted in patients to monitor physiological parameters. CardioMEMS, for instance, is implanted in one of the lungs of a patient to measure blood pressure inside the organ. It has been shown that patients with heart failure benefit from having such devices implanted.'



Stephan Achenbach MD graduated from the University of Erlangen Medical School in Germany in 1993. Today he is still there, as Professor of Medicine and chairman of its cardiology department. He has not only held posts in Erlangen, but also in Boston, Maryland, USA, and Giessen, Germany. With main clinical interests in interventional cardiology, general cardiology as well as cardiac imaging and intensive care medicine, Achenbach has authored around 550 publications listed in Medline. Between 2014-2016 he served as Vice President of the European Society of Cardiology (ESC) and is currently a Board Member and Chairperson of the ESC Congress Program Committee.

'We don't know how to control the monster we created'

Will software steal the heart of cardiology?

Celebrating 40 years of PCI, cardiologists fret over their future with big data, machine learning and robots, John Brosky reports

Software may replace cardiologists one day, but never the hands-on work of interventional cardiologists and their armatorium of hardware.

That was the curious consensus at the start of the 2017 EuroPCR congress, which saw the arrival of a robot performing catheter-based procedures and advances in computer-assisted diagnostic tools to aid guidewire operators with clinical decisions, such as whether to stent or not to stent.

This confident view among panellists at the conference came during a session dedicated to teasing out the 'Next Big Thing in Cardio-Vascular Medicine' at the largest European gathering of interventional cardiologists.

As with this year's congress of the European Society of Cardiology (ESC), the EuroPCR meeting celebrated the 40th anniversary of the first angioplasty procedure, which opened a new specialisation for interventional cardiology.

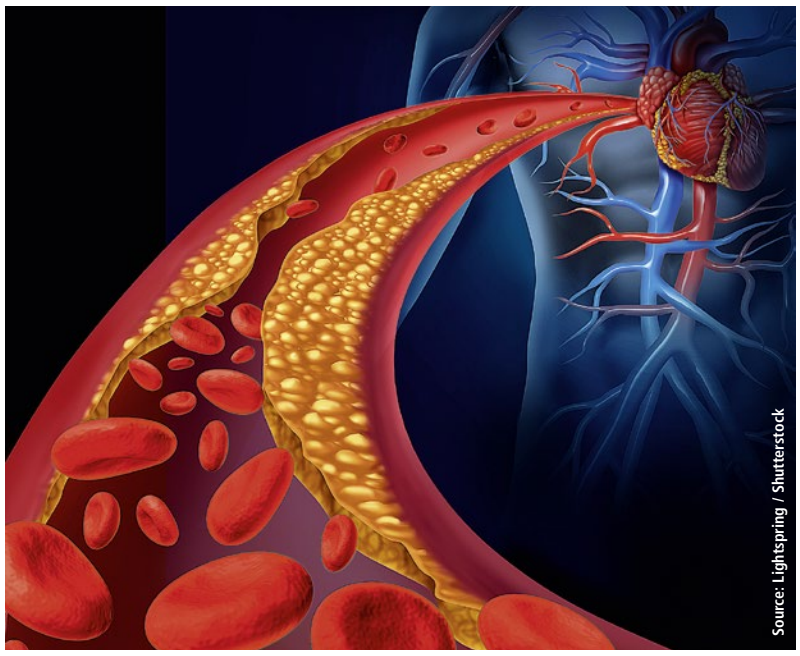
Many of the leading members of ESC are contemporaries of the pioneer for percutaneous coronary interventions (PCI), the German radiologist Andreas Grüntzig who re-opened a clogged artery using a hard wire catheter in 1977 at the University Hospital of Zurich.

Today there are almost 8,000 members of the European Association of Percutaneous Cardiovascular Interventions (EAPCI), making this the second largest of the associations within the legal structure of the ESC, surpassed only by the Heart Failure Association.

By 2015 the worldwide market for PCI had grown to $6.3 billion according to the Dublin-based firm Research and Markets.

Grüntzig's primitive tool opened what EuroPCR keynote speaker Stephen Oesterle called the vascular highway that enables interventional cardiologists, 'to go anywhere you need to go in the body.'

The field today covers 30 procedures that can be performed over-the-wire to place stents or treat vessels with drug-eluting balloons. And this does not take into account the growing practice of structural valve repair that is also performed over-the-wire.



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'Heart failure and mitral repair are two areas where developers are currently working to create catheter-based treatments,' he said.

Yet, we are still treating end-stage disease, he told colleagues, suggesting new catheter-based procedures could be developed for preventive strategies, such as implanting sensors to monitor blood pressure or glucose levels.

A practicing cardiologist for 25 years, Oesterle worked for 15 years

Continued on page 14

The simple, efficacious technique that revolutionised cardiology

Coronary angioplasty is 40 years old

Report: Mark Nicholls

Coronary angioplasty is arguably the most revolutionary breakthrough in the history of cardiology.

While the technique is today performed on millions of patients worldwide, its origins can be traced back to the work of Dr Andreas Grüntzig in Zurich, Switzerland, in the late 1970s.

Tragically, Grüntzig never lived to see the impact of his research, having died in a plane crash in 1985. Yet, across the world, his work has an enduring legacy and changed the face of cardiology forever. Later this summer – on 16 September - the world of medicine will be marking the 40th anniversary of the first coronary angioplasty.

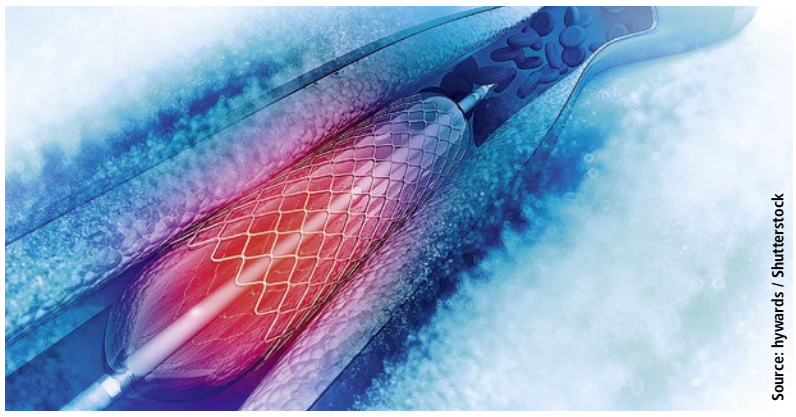
Before Grüntzig embraced the concept, others had experimented in the field. The technique of angiography was first developed in 1927 by the Portuguese physician Egas Moniz at the University of Lisbon for cerebral angiography while, in the 1960s, American interventional radiologist Charles Dotter pioneered angioplasty and the catheter-delivered stent, which were first used to dilate peripheral arteries by inserting sequential catheters with increasing diameters through the narrowing artery.

In 1958, Dr Mason Sones performed the first selective coronary angiogram and a few years later, Melvin Judkins introduced catheters shaped to reach the coronary arteries to perform selective coronary angiography.

It was this work that Grüntzig built on to perform the first successful percutaneous transluminal coronary angioplasty (PTCA) – or percutaneous coronary intervention (PCI) – on a human on 16 September 1977 at University Hospital, Zurich.

Born in 1939 in Dresden, Germany, Grüntzig studied medicine at Heidelberg University, graduating in 1964. He rotated through a series of internships in Mannheim, Hanover, Bad Harzburg, and Ludwigshafen, before moving to the department of Angiology at the University Hospital of Zurich in 1969.

His initial procedure used an expandable balloon based on balloons for use in peripheral arteries, created on a kitchen table in his apartment, helped by his assistant Maria Schlumpf. This was used on 38-year-old severe angina patient Adolph Bachman – the same age as Grüntzig. He successfully dilated a stenosed short non-branching section of the Left Anterior Descending (LAD) artery and presented the results of the procedure at the American Heart Association meeting two months later to widespread acknowledgement. Grüntzig performed coronary angioplasties on further patients in Zurich and taught the technique to other cardiologists, as the field evolved.



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Stent angioplasty procedure with placing a balloon

Contribution through example

Professor Tony Gershlick, consultant cardiologist at Leicester's Hospitals and Honorary Professor of Interventional Cardiology at the University of Leicester, reflects on Andreas Grüntzig's legacy…

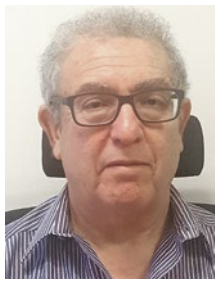
'Whilst not part of the original cohort who visited Grüntzig at the very beginning, my recollections of the procedure go back to an impressionable and formative age for me as a junior doctor at the National Heart Hospital in 1980, when Tony Rickards undertook what I believe to be the first UK balloon angioplasty patient.

'There was clearly a lot of excitement and undoubtedly something going on, so I decided I'd make a rare trip to the catheter laboratory. It was not possible… there were crowds of people.'

Inspired, Professor Gershlick became closely linked to the evolution of interventional cardiology, through the '90s – the decade of invention – and later was the first UK cardiologist to implant a drug eluting stent (DES) and first to implant a bio-absorbable stent. Awarded the inaugural British Cardiovascular Intervention Society (BCIS) Lifetime Achievement Career Award in January, recognising his 'outstanding contribution to the speciality of coronary intervention', he reflects on the door that Grüntzig opened. 'All of what we do now – radial day case intervention with great outcomes, especially in STEMI and even in complex surgical cases – would not be possible without Gruntzig's far-reaching insights. More important is the capturing of great minds and innovators by his original work. That legacy continues unabated today.

'He was a clinical scientist and his original studies taught us careful clinical studies, meticulous honest observations and robust reporting and interpretation of outcomes. Most importantly he never oversold the procedure.

'His contribution through example was and remains immense. Now, if by chance the first five patients had died - which was clearly a possibility considering the kit and lack of understanding regarding risk – then that would have been a completely different story. Maybe his real contribution was that in his hands, despite all, they didn't.'



Tony Gershlick is a consultant cardiologist at Leicester's Hospitals and Honorary Professor of Interventional Cardiology at the University of Leicester. For more than two decades he has been at the forefront of developments in interventional cardiology in the UK and was the first cardiologist in the UK to implant a drug eluting stent (DES) and a bio-absorbable stent. In January 2017 he was awarded the inaugural British Cardiovascular Intervention Society (BCIS) Lifetime Achievement Career Award in recognition of his outstanding contribution to the speciality of coronary intervention.

Naturally, there were complications, such as abrupt vessel closure after balloon angioplasty and restenosis but from the initial percutaneous balloon angioplasty; intracoronary stents were deployed in the mid-1980s.

Through the '90s and beyond, various incremental improvements in balloon and stent technology arrived, along with newer devices and medicine regimens resulting in the drug eluting stent, designed to help reduce in-stent restenosis. These also reduced the risk of stent thrombosis.

Coronary angioplasty is now the mainstay of cardiac care

One man who recalls those early procedures is Bernhard Meier, former Chairman and Professor of Cardiology and current Senior Consultant at the Swiss Cardiovascular Centre at Bern University Hospital. He worked with Grüntzig during the early development of the technique, and also 'found' the first patient to undergo the procedure.

Meier has been involved in coronary angioplasty as a specialist in interventional cardiology since the first case Grüntzig performed in Zurich 1977, having joined the team in 1976. 'I watched him doing peripheral angioplasty and helped him accumulate the respective data.

The former Chairman and Professor of Cardiology at the Swiss Cardiovascular Centre in Bern University Hospital, **Bernhard Meier** is currently Senior Consultant developing the centre into the most active for interventional cardiology in Switzerland. A close associate of Dr Andreas Grüntzig, Meier has been involved in coronary angioplasty as an interventional cardiology specialist since the first case in 1977. He was involved in the development of structural interventions such as closure of the patent foramen ovale (PFO) and the left atrial appendage (LAA), and in the introduction of transarterial aortic valve implantation (TAVI) in Switzerland.

I also suffered with him through more than a year of the desperate search for a patient suitable to become the first-in-man PCI recipient,' Meier recalled. 'Serendipity led me to find the first patient and assist Dr Grüntzig. Finding this patient when he was away and presenting the case to him upon his return was certainly one of my career highlights. 'I've been able to take care of this patient up to now. He's still doing extremely well, 40 years after his historical intervention, without ever needing coronary artery bypass surgery.'

When, in 1980, Grüntzig left Switzerland for the USA, Meier followed and spent three years with him in Atlanta, undergoing his cardiology training at Emory University.

Back in Switzerland, Meier further developed the technique as head of invasive cardiology at University Hospital, Geneva (1983-92). In 1992, he became chairman of the Cardiology Department at Bern University Hospital, turning it into the most active interventional cardiology centre in Switzerland.

Meier recalls Grüntzig (11 years his senior) as a role model: 'He was good looking, a sociable person, and full of great ideas with the necessary energy to pursue them even against a headwind from sceptics and envious – and sometime mischievous – colleagues and superiors.

'He also liked and lived simplicity as the basis of successful medicine. The balloon catheter to treat coronary artery stenosis is about as simple and as efficacious as it gets.

Will software steal the heart of cardiology?

Continued from page 13

with the medical device manufacturer Medtronic before joining the venture fund New Enterprise Associates, where he partnered Dr Scott Gottlieb who, in May 2017, was appointed new Commissioner of the USA's Food & Drug Administration.

Confounding the audience

When Oesterle shifted his talk from hardware to software he began to confound the audience.

The next big thing in the cardiovascular space, he said, is not in the room today – unless you count the smart phones in everyone's pocket.

The research and development budget at Apple is $17 billion annually, and what they are working on will make the future iPhone a healthcare companion, he said.

Google Life Sciences, now called Verily, has invested $4 billion over the past two years to create partnerships with Johnson & Johnson's surgical division and glucose monitoring specialist Dexcom, as well as several major pharmaceutical companies.

IBM has declared that healthcare is the future of the company, he said, and the Watson super-computer is not meant to play games, having already shown it can outperform radiologists.

Data analytics coupled with cognitive computing will take over healthcare, Oesterle predicted. 'We have come to a point where computing power is massive, it is fast and it is incredibly cheap. Your next-generation competitor will come from software.'

As a venture capitalist, he noted that less than 10 percent of private equity funding goes to medical technologies, that 20 percent goes to biotechnologies and '70 percent goes into the software that is going to disrupt our practice, just as it has disrupted other industries.'

'No one wants to back a new stent, distributed healthcare is where the money is going,' he said, adding that consumer-oriented medical technologies aim to pass up the clinician in order to go directly to the patient.

Vice President for Medical Affairs at Medtronic Vascular, Martin Rothman spoke up to say: 'I just can't see these next big things.' And he agreed the next big cardiovascular enterprise based on software would not be Medtronic. 'It's not our core skill. We do some software engineering but what we really do is micro-engineering and that is our skill.'

Then he added: 'When we talk about what will be the next big application in data handling, we quickly come to the important question: Where is the revenue? When we sell a stent or a TAVR [transcatheter aortic valve replacement], we get revenue. How do you get revenue when you sell a software click? How do you make that work? We don't understand it,' he said.

With the authority of his white-haired seniority, Eberhard Grube, the Chief of the Department of Cardiology and Angiology at the Heart Centre in Siegburg, Germany, followed up on these comments: 'We are speaking of things that may come in 20 years. It makes me dizzy talking about five billion here and 50 billion there.

'Perhaps,' he suggested, 'we are more down-to-earth.' Then he cautioned colleagues, 'We hear about an unlimited imagination in what software can do, and then we look at what happened with a hospital in the United Kingdom when it no longer had access to its data. We have created a monster we do not know how to control.'

Improved monitoring and raised quality of life

Intelligent shirts 'watch' cardiac patients

A pioneering study has certified that wearable technology produced better results in monitoring cardiac patients and improving their quality of life compared to conventional systems. European Hospital correspondent Mélisande Rouger spoke with Spanish cardiologist David Del Val MD, who led the study, before he presented his results at the European Congress of Cardiology held in Barcelona.

David Del Val: 'Medicine, and more particularly cardiology, is experiencing a real technological revolution. Many devices have been developed to improve diagnostic therapy efficiency and patients' quality of life. However, very few studies have actually measured the pertinence of these devices in real life. This study is a pioneering work because it compares efficiency in a new wearable device and conventional systems in clinical practice.

'The study was designed to compare monitoring efficiency in terms of perceived life quality benefits in patients using a wearable system developed by a company called Nuubo and conventional electrocardiographic monitoring systems.

'150 patients alternatively used intelligent shirts and a conventional ambulatory monitoring system to monitor their cardiac rhythm during 24 hours.

'Results showed that the effective monitoring time was higher with the new system using wearable technology compared to the conventional system. Questionnaires answered by patients also revealed that quality of life indices were higher in those who used a wearable device.

'Our cardiology department started work with Nuubo's technology five years ago. We have worked with the same company on other projects to evaluate prolonged electrocardiographic monitoring over a week and a month, and electrocardiographic monitoring on sportsmen during competitions. We obtained very positive results in both projects.

'Personally I have always been very interested in medical technology advances, especially for cardiology; that's why I seized the opportunity to lead the first clinical experiments with Nuubo's monitoring system.'

Are collected data then stored in the patient's electronic health record?

'The data generated by these devices is stored on a memory card and can be downloaded and analysed thanks to dedicated software. We write a report based on this data, which is kept in the patient's health record. Unfortunately, in our hospital, there isn't any system enabling connection and incorporation of this data directly into the electronic clinical history, which doubtlessly would be a great advance.'

Are you or your colleagues working on other wearable technology projects?

'For the moment, I'm not involved in other projects validating wearable technology, but I consider this to be a field with major projection for patients suffering chronic diseases.

'Our cardiology department is currently working on a cutaneous patch that enables continuous medication of different haemodynamic parameters, a system that can help to follow up patients more closely and anticipate the disease progression.

'The department also leads another project in which a toothbrush enables us, daily, to measure vital signs and various biomarkers in the saliva.'

'Wearable technology enables us to remotely follow up different key parameters early, to detect any worsening of a given pathology. Therefore, we can anticipate and plan our actions to fight the disease, initiate early treatment, avoid hospitalisation and reduce healthcare costs.

Cardiologist **David Del Val MD** is currently completing his fellowship in haemodynamics and interventional cardiology at Ramón y Cajal University Hospital in Madrid, Spain. Having gained his medical degree from Madrid Autonomous University his residency in cardiology was at Ramón y Cajal Hospital. Later, at Alcalá University, he specialised in scientific investigation methodology.

We must protect cardiologists from cancer risk

CorPath enters the vascular highway

Shielding cardiologists from harmful radiation is the goal for two systems capable of navigating the vascular highway, John Brosky reports

'We cannot continue to accept working in conditions that put our lives in danger,' says Alain Cribier, the pioneering cardiologist from the University Hospital of Rouen, who first implanted an aortic heart valve via a catheter in 2002. 'You don't feel anything; radiation is not painful, but there is an accumulation of dose when you do this for decades, day-in and day-out,' he explained.

A study, published by the American Heart Association in August 2016, demonstrated a direct relation between working in a catheterisation lab and developing radiation-induced cancer, cataracts and skin lesions.

According to the study, interventional cardiologists accumulate significant lifetime radiation exposure in the range of 50 milliseverts to 200 mSv, which corresponds to a whole body dose equivalent to 10,000 chest X-rays.

'I have lost several colleagues to brain cancer,' Alain Cribier told European Hospital. 'We all have musculoskeletal problems,' he said, bringing out of a closet the 12-kilo lead apron he wears during 12-hour work shifts that can result in aggravated orthopaedic maladies.

At EuroPCR in May 2017 in Paris, Cribier met with fellow cardiologists on the stand of Robocath, in his role as a key opinion leader for the company, which is also based in Rouen.

He discloses that he has no financial interest in the company but an enthusiasm for a system that can put a shielding wall between him and the irradiating X-ray projector that, as he points out, hovers just inches from his head during some time-long procedures.

The R-One system from Robocath is not the first remote stenting robot for cardiology.

Two systems approved by the USA's Food & Drug Administration are commercialised by Corindus, based in Waltham, Massachusetts, which during EuroPCR 2017 celebrated what it called a milestone for the 100th percutaneous coronary intervention (PCI) performed using the second generation CorPath GRX System.

Although Corindus systems hold a CE Mark, the company has yet to sell a CorPath robot in Europe.

Robocath is currently completing pre-clinical trials as part of its submission for a CE Mark approval that it hopes to receive in 2018. A submission of the device to the FDA is expected in 2019.

The results of a single-centre REMOTE-PCI [percutaneous coronary intervention] study sponsored by Corindus were published in the January 2017 edition of EuroIntervention, the journal of the European Association of Percutaneous Cardiovascular Interventions (EAPCI) and the European Society of Cardiology (ESC).

PCI was successfully performed on 19 of 22 target lesions using radial access, the first demonstration of the ability to perform PCI from outside the confines of the cath lab by using a combination of robotics and telecommunications.

The CorPath 200 cockpit to control the robot was installed in a separate room, roughly 17 meters from the patient table, isolating the operator but maintaining continuous video and audio contact with both the patient and any personnel in the lab.

Principal investigator Ryan Madder MD, a cardiologist and researcher with the Spectrum Medical Group based in Grand Rapids, Michigan, told European Hospital that, in addition to the stenting procedures, he has successfully utilised the CorPath robot to perform the diagnostic procedure of fraction flow reserve (FFR) to assess lesion severity.

Potentially, Madder said the remote robotic system can be installed anywhere there is a fluoroscopy suite, and that it suggests a potential for tele-stenting, an ability to perform procedures in regions where PCI is currently unavailable by utilising a robotic cockpit located in a distant expert centre.

'We are still very early in this study; there's a lot of work to be done,' he noted. 'We are ways off from deploying a system to community hospitals.'

Neuroradiologist Philippe Bencteux, is the founder of Robocath, based in Rouen, France.

Prof. Alain Cribier, MD, is head of Cardiology at the Charles Nicolle Hospital , in Rouen University, France.

Back at the R-One robotic system from Robocath, Cribier provided a demonstration. 'This is not a totally new idea,' he said. 'There are surgical robots, orthopaedic robots, robots for brain surgery. But it was not considered possible for cardiology. I was sceptical myself but, over 10 years, I have followed the progress step-by-step as they solved technical problems.'

At the patient table, Cribier feeds the catheter into a single-use cartridge, an integral part of the robotic mechanism that contains the graspers that advance and turn the guidewire.

Walking from the patient table to the control panel behind a radiation shield, he said, 'The robot does not perform anything itself, everything is controlled by the operator's hand,' he pointed out. 'I can do exactly the same things using the robot that I would do with my hands, advance the wire, retreat, rotate and push.'

At the controls he advances and rotates the guidewire simultaneously, pushing and turning, something the CorPath robot cannot do.

Cribier expects in a next step the robot can be applied to peripheral artery procedures as it uses the same sized wire. Corindus has already been granted an extended indication by the FDA to apply the CorPath for peripheral procedures.

As for the transcatheter aortic valve replacement procedures that he pioneered, Cribier said, 'There is no question the system can be adapted to accept these larger catheters. This system will allow physicians to go anywhere on the vascular highway.'

We must embrace the potential of digital data

Cardiologists must keep up

Tex vector / Shutterstock

Report: Mark Nicholls

Leading cardiologist and healthcare researcher Professor Harlan Krumholz has warned that medical practitioners must embrace the potential of digital data generated by patients if they are to avoid being left behind as the digital revolution moves forward at an ever-advancing pace.

As Professor of Medicine (Cardiology) at Yale School of Medicine, he delivered the prestigious Paul Wood Lecture at the June conference in Manchester, UK, of the British Cardiovascular Society on a theme of 'Personalised medicine and computational cardiology – enhancing cardiovascular care and health in the next era'.

'Data generated every day for a variety of practical purposes can serve as an inexhaustible source of knowledge to fuel learning in a healthcare system,' he said, but warned that if medicine wants to take advantage of technology, it has to catch up with the digital revolution. He pointed to statistics that show the average American spend 5.6 hours on digital devices every day, including those in older age groups, and that medicine has to recognise the power of this trend.

Krumholz also suggested that medicine has not learned to communicate as rapidly, effectively and simply with its audience in the way that other sectors, such as weather forecasters, retailers, and traffic bulletins, have. Medicine, he said, had been slow to find ways of integrating digital data into practice, pointing to the transition to electronic health records, where he feels health professionals in the USA were slow to get involved as hospitals made the transition - eased with $50bn of funding. In 2008, 9.4% of records were electronic health records (HER) but, by 2015, it was 83.8%.

He also felt patients should have access to their own record to share it in ways that can improve their care and augment research, being partners as 'citizen scientists'.

The most important element about precision medicine, Krumholz continued, is that it can be driven with patients as partners and that the doctors and researchers should recognise the value of patient reported outcome data that are generated from wearable

An exciting new approach for heart bypass surgery

Transforming veins into arteries

Raimondo Ascione is Professor of Cardiac Surgery and Translational Research at the University of Bristol, UK. He is also Academic Director of the pre-clinical Translational Biomedical Research Centre (TBRC), which bridges the gap between basic science research and the NHS to boost the translation of fundamental discoveries and emerging biomedical technologies to the bedside. Ascione is also Chief Investigator of clinical trials and experimental work aimed to protect adult high-risk patients from complications during cardiac surgery.

Report: Mark Nicholls

Scientists in the United Kingdom are investigating the potential of a new regenerative and tissue engineering technique that could transform veins into arteries to improve the outcomes for patients undergoing heart bypass surgery.

The research, at Bristol University, led by cardiac surgeon Professor Raimondo Ascione, alongside Professor Sarah George and Dr Jason Johnson, could revolutionise the approach to cardiac artery bypass surgery.

Presently, replacement arteries for bypass operations are limited, so surgeons use veins taken from the patient's leg to replace the blocked vessels of the heart.

Populating veins with artery-like cells

However, while arterial grafts can continue to work well for up to 20 years, up to half of vein grafts can become blocked within 5-10 years as the greater blood pressure of the artery environment damages the graft after implant. 'With the bypass surgery we are taking a piece of vein from the leg which has a thin wall with blood flowing at a very low pressure,' explained Professor Ascione, Chair of Cardiac Surgery and Translational Research at Bristol. 'But when put into the heart it has to support and sustain a much higher pressure because it is being put into an arterial system, a high pressure system, so this is what leads to problems with the vein.

'Currently, veins are used for approximately 80% of all grafts made during heart bypass surgery. They work well in the short-term, but they are not designed for the demands of working as an artery.'

This may result in the grafted vein thickening its wall and becoming blocked and, when this happens, the heart bypass operation may have to be repeated, or the patient may even suffer a heart attack.

The Bristol team aim to achieve the vein-to-artery transformation by 'washing' cells from the vein, stripping it back to leave a tube-like scaffold made from extracellular matrix. An artery can then be built on this framework by populating it with arterial-like cells. This will be done either before surgery, in a dynamic bioreactor that mimics the arterial environment, or after the surgical implant by the host's natural healing processes.

'With the old cells stripped out of the vein we are only left with the vascular skeleton, the actual framework of the vein,' Ascione explained. 'The vein goes from being "pinky" to like a white ghost colour. Then we can use this acellular skeleton of just vascular extracellular matrix and transform it into a high-pressure system and seed the arterial cells on this.

Tissue-engineered arterial grafts improve long-term outcomes

'By stripping back a vein and using it as the framework on which to build an artery, we hope to create in the lab tissue-engineered arterial grafts that are better able to cope with the demands of carrying blood from the heart.'

The professor has already demonstrated the feasibility of these approaches in pilot studies and is now leading a new project to find the best method to re-populate the tube-like scaffolds derived from veins with cells.

Plain and pre-populated scaffolds will be implanted into pigs at the new Translational Biomedical Research Centre (TBRC) co-funded by the British Heart Foundation (BHF) and the Medical research Council (MRC) to establish if they give a better result than the grafts that are currently used. If this proves successful, it could see a new approach to the way heart bypass surgery is performed. In future, the vision is that patients would be admitted to hospital a few weeks before their operation for veins to be taken from their leg and engineered in a laboratory into arteries.

The patient would return to hospital a few weeks later for bypass surgery operation with surgeons using the vein material that has been transformed into arterial-quality conduits.

'In terms of surgical technique, it would be pretty much the same,' Ascione added. 'Stitching and suturing these arterial-like grafts will be similar to those grafts surgeons are already used to, so no further training would be necessary.'

The technique could also benefit vascular surgeons who, for peripheral vascular grafting in patients with blocked arteries in their legs, can only use vein or synthetic material with poor mid-term outcome.

Around 17,000 coronary artery bypass operations are carried out in the United Kingdom each year, with many thousands more conducted internationally.

This approach could improve longer-term outcomes for heart bypass patients.

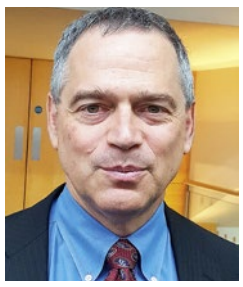
'Ultimately,' Ascione concluded, 'this research could mean that people receive longer-lasting grafts, improving their life expectancy while reducing their need for future surgery and use of hospital resources.'

devices and data collection mobile technologies.

Suggesting that data acquisition is an important new dimension to the way doctors approach medicine, Krumholz said: 'Medicine now is more than ever an information science and increasingly a digital information science.' Yet he harbours concerns about whether physicians are truly making the best use of available data unless they 'learn to use and develop new knowledge iteratively' and acquire 'smart enough' systems to process the data and utilise it.

Among his key concerns is that current medical research enterprises cannot keep pace with the information needs of patients, clinicians, administrators and policymakers. The digital revolution, tools and approaches, he pointed out, could augment and accelerate knowledge – producing a new paradigm of a learning healthcare system. 'Medicine needs to realise that we are in a new era,' he said. Health professionals, not the technicians, have to be the key, as they understand what patients need and the complexity of the problems that our patients face.

'The next generation must be deployed in a way that preserves the special nature of our profession but the advances in technology should help us be better, not replace the human touch. We should not be afraid of technology when it comes to health. It is better to embrace it - it can make us smarter than ever in looking after large populations.'



Cardiologist **Professor Harlan Krumholz** is a healthcare researcher at Yale University and Yale-New Haven Hospital, and the Harold H Hines, Jr. Professor of Medicine and Director of the Yale Center for Outcomes Research and Evaluation (CORE) – one of the America's most productive research units dedicated to producing innovations to improve patient outcomes and promote better population health. He is also a Director of the Robert Wood Johnson Foundation Clinical Scholars Program, which prepares especially talented physicians to become future healthcare leaders.

New scan detects inflammation after heart attack

Exciting hyperpolarised MRI

Report: Mark Nicholls

A new type of scan that can detect cardiac inflammation may help tailor treatment for patients who have suffered a heart attack, according to research findings presented at the British Cardiovascular Society (BCS) conference in June. Developed in the UK, hyperpolarised MRI (h-MRI) enables cardiologists to see more detail of healthy and diseased hearts than conventional scans, including the level of inflammation post-myocardial infarction.

Detecting inflammation in the heart

Funded by the British Heart Foundation (BHF) the University of Oxford researchers now believe h-MRI could help scientists develop and monitor the effects of new, inflammation-targeting treatments that may improve the heart's healing process in heart attack patients.

The discovery could have significant benefits because the hearts of patients who have suffered a myocardial infarction (MI) can undergo continued inflammation even during the healing process, and despite receiving emergency treatment.

Yet research into why this may happen remains limited as conventional scans cannot detect or measure inflammation in the heart, whereas h-MRI can.

Conventional MRI measures how protons change position when exposed to a magnetic field, but h-MRI works by producing images from carbon molecules, which make up the energy sources needed to help the heart pump and can offer doctors a clearer picture of inflammation in the heart.

h-MRI as biomarker and pharmacological target

The Oxford University team used the hyperpolariser laboratory to investigate how the experimental drug 2-deoxyglucose (2-DG) may improve heart function after a heart attack

For the study, the team measured production of lactate in the damaged heart tissue of rats and found that after a heart attack immune cells within the injured heart muscle become active and are reprogrammed to make lactate, leading to inflammation in the heart. By monitoring how much lactate is produced in the damaged tissue, they were able to identify and measure the level of inflammation in the heart.

Following on from that, the team administered the experimental drug 2-deoxyglucose (2-DG) to the rats after the heart attack, to try and combat the inflammation.

Using h-MRI to monitor the heart's response, they found that 2-DG reduced lactate production and inflammation, and improved the heart's function.

The cutting edge scanning system

They showed that high hyperpolarised lactate signal in the days after myocardial infarction is caused by macrophage-driven inflammation, and reflects not just the number of inflammatory cells infiltrating the myocardium but also the inflammatory phenotype of those cells.

The Oxford scientists – one of the first groups to use h-MRI to study the human heart – believe that h-MRI will not only detect inflammation in damaged heart tissue but also could provide a novel method for the detection of myocardial inflammation with high translational potential as both a biomarker and novel potential pharmacological target.

'H-MRI is a cutting-edge scanning system which allows doctors to better understand the innermost workings of the heart non-invasively, and how they become abnormal in heart disease,' Dr Andrew Lewis, Specialist Registrar in Cardiology at the Great Western Hospital in Swindon, summed up. 'In this research, we used h-MRI imaging to capture the healing processes in experimental models after a heart attack, and also tested new treatments to improve the heart's recovery.

Andrew Lewis MD is a Specialist Registrar in Cardiology at the Great Western Hospital in Swindon, UK, and won the Young Investigator's Prize Competition at the British Cardiovascular Society conference in Manchester for his research into myocardial inflammation imaging.

More studies needed

'Our work has identified several forms of heart disease where this technique could be used to improve diagnosis and treatment,' Lewis added. This is incredibly exciting, and we intend to move forward with patient studies as quickly as possible.'

Lessons gained from an EHRA 2017 Symposium

Cardiac resynchronisation therapy improvements

Which CRT patients can be 'downgraded' from a CRT-D device with defibrillator function to a CRT-P with just a pacemaker function? This, with two further current CRT issues – chronotropic incompetence and telemonitoring of CRT patients – featured prominently at the Europace-Cardiostim Congress in Vienna.

For more than 20 years, cardiac resynchronisation therapy (CRT) has been a pillar in the treatment of chronic heart failure (CHF). CRT devices are either pacemakers (CRT-Ps) or implantable defibrillators (CRT-Ds), which are implanted in the patient's chest. These are connected to the heart with three leads, the third one linking to the left ventricle which pumps blood through the body. While both types of devices synchronise the heartbeat, CRT-Ps prevent the heart from beating too slowly and CRT-Ds prevent it from beating too quickly.

At a satellite symposium at the Europace-Cardiostim Congress (EHRA 2017) experts debated whether patients who respond well to a CRT-D and show improved heart function should receive a CRT-P in the next scheduled device replacement. The background: Many patients respond so well to CRT that their heart function markedly improves and a CRT-D might not be needed; indeed between 10-25% are so-called super-responders, i.e. their cardiac device restores a normal ejection fraction in the left ventricle, lowering the risk of sudden cardiac arrest to that of a healthy person.

At EHRA 2017, Dr. Jacques Mansourati from Brest University Hospital in France, presented a study investigating this very issue: The BioContinue study is observing 277 CRT patients in eight countries to determine which patients need a defibrillator. According to preliminary study data, 39% of patients who receive a CRT replacement do not need a defibrillator because the therapy increased the ejection fraction of the left ventricle by at least 40% and no ventricular tachycardia was reported. 'During a scheduled replacement of the device, responders and super-responders can be downgraded from a CRT device with defibrillator to one without this function,' Mansourati explained.

The second controversial issue in CRT is chronotropic incompetence: In 20-40% of all CRT patients, heart rate does not increase commensurate with increased physical activity. 'Chronotropic incompetence could be a major factor in patients who do not respond to CRT,' said Dr. Mattias Roser from Charité Berlin. In these cases, Roser points out, rate-adaptive pacing might provide a solution, as indicated by BioCreate, a pilot study conducted at Charité to investigate whether Closed Loop Stimulation in heart failure patients with chronotropic incompetence can improve clinical outcomes. This technology, developed by Biotronik, responds naturally to patients' physical and mental activity or stress, adapting heart rates physiologically.

Roser is optimistic: 'We consider this a highly potential approach to significantly improve the treatment of CRT patients,' he said.

The third, but by no means least, important issue is remote monitoring of ICD patients. Ever since the IN-TIME study showed Biotronik Home Monitoring reduced mortality in heart failure patients, the use of this technology has been included in the clinical guidelines. However, data presented at EHRA 2017 indicate that not all tele-monitoring systems are created equal: they do offer different clinical outcomes. TRUECOIN, a meta-analysis, showed Biotronik Home Monitoring to reduce mortality in all types of ICD patients.

Where will material come from as demand grows?

Renewing the promise of bioabsorbable implants

Electrospun materials bring a spark of hope to a cardiovascular landscape darkened by setbacks for reabsorbable stents, John Brosky reports

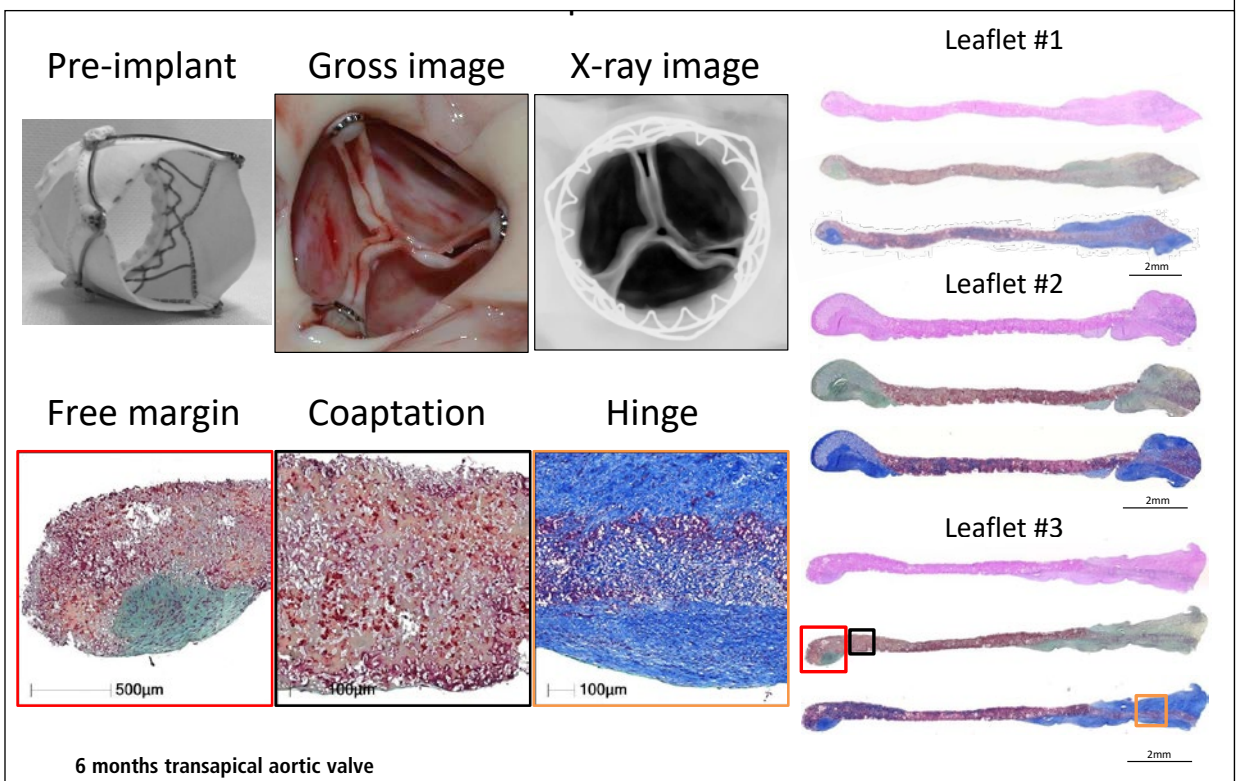
It was famously said that implanting a device in a person to cure a disease is to implant a new disease. Simply put, the human body will continually fight against foreign materials, leading to chronic inflammations or repeated interventions. Which explains the recent excitement among cardiologists for a new generation of materials that can repair a diseased condition, and then disappear as the body absorbs the foreign material.

The earliest advances in this field were made with bio-reabsorbable stents (BRS), which have also delivered the greatest setbacks. Two- and three-year results for the leading stent, the Absorb BRS from Abbott Vascular, not only failed to demonstrate the promised benefits, but also in some trials showed a dangerous tendency for in-stent thrombosis. In the August 2017 issue of EuroIntervention, Editor-in-Chief Patrick Serruys noted the long-term follow-up data from randomised trials 'sometimes contradict themselves', and show that, 'we went from the best result to the worst result.'

With improved technology, he concluded, 'We will reach the promised land, which is not for tomorrow but for the day after.'

Beyond stents, which utilise a hardened bioabsorbable polymer, other cardiovascular applications for bioabsorbable materials have shown more promising long-term results with the first in-human trials.

The technology that may open a new path to the Promised Land is electrospinning, where an electrospray technique combined with the spinning of fibres creates a highly versatile soft fabric for implantation devices that the body can absorb over time.



6 months transapical aortic valve

While this technology has been known for 100 years, and for decades has been used to produce absorbable sutures for surgical closings, it is only recently that new devices using the materials have emerged.

According to Benoit Studlé, the CEO of Statice, which designs and manufactures these next-generation cardiac implants, the rediscovery of this technology is due to a progressive evolution in the savoir-faire for engineering unique chemical and mechanical properties.

'The medical need has been better defined, which has created a greater demand, and as a result, there is a market today. This is a great motivator,' he said, adding that there are multiple projects moving in the cardiology pipeline.

As a contract manufacturer, Studlé can not speak about projects being developed by innovative physicians and start-up entrepreneurs at Statice – except to say the company is a partner in a pan-European program TEH-TUBE, [tissue engineering of the right heart outflow tract by a biofunctionalised bioresorbable polymeric valved tube] and REVAMED, a €4 million program to develop implantable biosynthetic patches for drug delivery to aid with surgical closings, wound dressings and pain management.

Statice engineers are also creating electrospun fabrics for an aortic valve, but this is still in an early stage of development.

A Swiss firm that can speak publicly about its work in cardiovascular applications is Xeltis, which, during EuroPCR 2017, renewed the hopes for bioabsorbable implants in a crowded scientific session.

Xeltis presented the 24-month results for a pulmonary heart valve to correct or reconstruct right ventricular outflow tract in 10 children, as well as the first study results from the company's preclinical aortic valve program.

The prestigious panel of key opinion leaders would have been enough to pack the room, as it included presentations by Serruys, who is a professor of Cardiology Imperial College London; Thierry Carrel, from the University Hospital Bern Clinic, who also serves on the editorial board of several international journals; the internationally renowned cardiovascular pathologist Renu Virmani; and, Martin Leon, the director at the Center for Interventional Vascular Therapy at Columbia University Medical Center and New York-Presbyterian Hospital.

Elazer Edelman, who directs the Harvard-MIT Biomedical Engineering Center and is a member of the U.S. FDA's Science Board, chaired the session.

The Chief Technology Officer and co-founder of Xeltis, Martijn Cox, explained the principle of what his company calls endogenous tissue restoration using electrospun fabrics.

The human body colonises implanted scaffolding by creating proteins and collagen to build new tissue, while macrophages also attach to the structure and simultaneously dissolve the foreign material.

Serruys suggested the dynamic tension between the rate of destruction and the rate of construction would be the subject of debate for a long time.

'How sharp, how long, how fast? There may yet be surprises, we may discover new enemies,' he said.

Virmani showed that among the children implanted with the Xeltis valved conduit, the diameter of the valve is not only well-maintained after two years, it is enlarging, 'so that as the child will grow, this conduit will allow enlargement of the pulmonary trunk as well as the valve'.

Yet, a conduit is not an aortic valve, she said, showing histological evidence to demonstrate a critical inconsistency in the creation of new tissue at the hinge point of the aortic valve. 'We need to think completely differently about how colonisation and tissue formation is achieved,' she said. 'Unfortunately, we cannot learn this on the bench top

The promised land of synthetic implants that can heal is clearly not for tomorrow.

Yet, as Edelman noted, there is urgency in cardiovascular interventions. 'Today heart valves are made from the hide of a very small herd of animals in a very small part of the world. This forces us to consider where these materials are going to come from, as the demand grows greater,' Edelman pointed out.

According to Leon, in a summary statement: 'This innovative treatment approach has the potential to reduce complications, re-interventions and healthcare costs, while improving quality of life for patients with heart valve disease. This would represent a major leap forward in heart valve therapy.'

Supporting women in electrophysiology and cardiology

The EPIC Alliance

'We are now in an era where patients with implantable devices – not just pacemakers, but also cardioverter defibrillators – can undergo MRI scanning. Although there are still open questions, we no longer have to exclude these patients from this very important imaging technology,' said Seattle-based cardiologist Professor Jeanne E Poole, during the Europace-Cardiostim Congress (EHRA 2017) in Vienna. While discussing implantable devices and MRI is not unusual at a scientific congress, the satellite symposium 'Clinical Decision Making in Electrophysiology/Arrhythmias', chaired by Professor Poole, differed from other such events in one particular way: the panel was all-female. This symposium was organised by the Electrophysiologist International Community Alliance (EPIC Alliance).

Founded in 2010, the EPIC Alliance aims to advance career opportunities for women in electrophysiology and cardiology. The network currently includes 250 women electrophysiologists and cardiac device specialists internationally. 'It is focused on helping women achieve a pathway in electrophysiology equally as successful as men,' Poole pointed out.

First and foremost, the founders of the EPIC Alliance wanted to create a network for women working in electrophysiology and cardiology. 'Globally, we did not know each other; many of the female electrophysiologists and cardiac device specialists had not met women from other countries working in this field,' Poole explained during our interview.

Today, EPIC Alliance activities have moved far beyond the initial networking aspect to provide members with an array of professional development opportunities. Members are supported in submitting abstracts and organising symposia at conferences; experienced mentors share their knowledge and support young and upcoming physicians; the alliance also organises meetings and networking events for members to gather at global and local levels. 'The EPIC Alliance is the most successful organisation supporting women in our field, in which very few women work,' said Poole, estimating that only about 10 percent of all electrophysiologists and cardiac device specialists are female.

Women, she surmises, may be put off by the two to three years of additional training and by extremely long working hours, two factors that appear to be irreconcilable with motherhood and family. However, Poole herself provides a convincing example that a satisfactory work/life balance can be achieved. 'But,' she underlines, 'we do need role models and we must ensure women are visible at scientific congresses.'

Male colleagues, she added, would also benefit from a sustainable work/life balance: 'We are all just human beings working in a very exciting speciality.'

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MEDICA LABMED FORUM

13 – 16 NOVEMBER 2017
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Early detection of cancer and cardiovascular diseases

Monday, 13 November 2017: Oncology –
Can cancer be detected by a blood test?

Tuesday, 14 November 2017: Cardiology –
More diagnostic confidence with myocardial infarction and heart insufficiency

Prof. Dr. med. Stefan Holdenrieder, Deutsches Herzzentrum München

The laboratory comes to the patient

Wednesday, 15 November 2017: Diabetology –
From self-test to continuous glucose measurement

Prof. Dr. med. Peter Luppa,
Klinikum rechts der Isar der TU München

Dangerous travel companions

Thursday, 16 November 2017: Infectiology –
New multi-resistance in the age of migration

Priv.-Doz. Dr. med. Beniam Ghebremedhin,
Universität Witten/Herdecke, HELIOS Universitätsklinikum Wuppertal

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Exposing activities in wayward hearts

Biomarkers are diagnostic game changers

Providing insights into new cardiac testing methods, Professor Stefan Holdenrieder, Director of the Institute of Laboratory Medicine at Munich's German Heart Centre, explained why biomarkers are a game changer in diagnostics.

Interview: Daniela Zimmermann

Professor Holdenrieder: 'Obviously the good news is that sensitivity, and thus the quality of biomarker tests for the early diagnosis of cardiac diseases, is constantly improving. Moreover, the change of marker levels and combinations of markers are increasingly used in diagnostics to obtain even more precise results.'

Does this mean diagnostics is like a veritable orchestra with various instruments?

'Correct. With regard to cardiac diseases new biomarkers, such as copeptin, are on the rise, complementing troponin since they provide results faster – an important factor particularly in the emergency room.'

But troponin is here to stay?

'Absolutely, particularly since today we have highly sensitive troponin tests that can diagnose a myocardial infarction within half an hour.

'The crucial advantage of highly sensitive tests is the fact that they measure even low values very precisely. Troponins take a while, until they increase significantly.

'Before, a patient with symptomatic chest pain, but unsuspicious ECG and unsuspicious troponin values had to wait for about three hours until a new test showed the troponin changes. The new and highly sensitive tests can show changes after only an hour – if a myocardial infarction has happened.

'This allows us to either intervene early or, if the values are unsuspicious, confirm that there was no cardiac event and we can send the patient home. This new type of test is faster and more precise. Equally important – with the help of troponins we can detect previous damage to the heart.'

These highly sensitive tests are not yet available in Germany?

Indeed. Having said that, many medium size labs are already equipped with the analytic tools required for these tests. Processing the tests is simple and not particularly expensive. Nevertheless, there are places where the tests cannot yet be applied, such as in your doctor's (GP's) surgery. Today, no POCT units are available that can use these highly sensitive tests. The development of such POCT tools will play a major role in the future.'

Since troponin can be measured with such high precision, will other markers, such as copeptin, still be needed?

'Yes, in the case of a disease we try to intervene as early as possible. There is still a gap between the onset of symptoms and detection of troponin, or rather the onset of the therapy. During this time gap there is a risk of the coronary vessels being obstructed. Copeptin can help us get through this phase because it's a pro-hormone, which, in a stress situation, is released by the hypophysis within minutes.

'Obviously the stress can be triggered by a number of events, be it an accident, inflammation or infarction. Usually copeptin is already elevated when troponin is still unsuspicious. Thus copeptin gives us important time to prepare treatment. While the marker does not confirm the diagnosis myocardial infarction it does offer an important warning signal of a cardiac event. 'If, by the same token both copeptin and troponin values are unsuspicious, we can say with 99 percent likelihood that no myocardial infarction happened.'

Highly sensitive troponin tests can diagnose a myocardial infarction within half an hour.

Source: Pruser/shutterstock

Where else can biomarkers be used?

'In cardiology there are two reliable biomarkers that indicate cardiac insufficiency: the peptide BNP and the precursor fragment NT-proBNP. Both indicate the degree to which the heart muscle cells are stretched. Increased myocardial wall tension is a clear indicator of cardiac insufficiency. Increased markers are a serious alarm signal. However, for the initial diagnosis it is irrelevant which marker is being measured.

BNP has a shorter half-life in the blood, thus the NT-proBNP value is more precise. With acute heart failure, though, both values are increased. Moreover, both values are used for risk assessment and follow-up. Since certain therapies affect BNP metabolisation, NT-proBNP is the marker of choice to measure outcome: When NT-proBNP decreases, the therapy is effective. Further promising markers are in the pipeline, such as ST2, galectin-3 or GDF-15.'

What role will biomarkers play in the future?

'The potential of biomarkers is far from exhausted. Currently a number of studies are investigating which biomarker categories can be used for which types of clinical issues. Generally speaking, biomarkers can play a role in genetics, epigenetics, with micro-RNAs or exosomes, lipids, proteins or as metabolomic markers, or any combination of biomarkers. There are many and various possibilities.

'We are charting new territory here and further exploring the potential will require large-scale studies and handling of huge data volumes.

New diagnostic technologies open up new horizons with regard to understanding the development of arteriosclerosis and cardiovascular disease. However, meticulous assessment of diagnostic findings is crucial to determine a suitable treatment that will help the patient.'

With previous roles at the Institute for Clinical Chemistry and Clinical Pharmacology at Bonn University, and the Institute for Clinical Chemistry at Munich University, today **Professor Stefan Holdenrieder** is the Director of the Institute of Laboratory Medicine at Munich's German Heart Centre. His research focus lies on the development and evaluation of new laboratory diagnostic biomarkers and technologies for cardiology, oncology, immunology and neurology, with an additional special focus on circulating nucleic acids and their genetic and epigenetic changes.

MEDICA's LABMED Forum

13-16 November. Dusseldorf, Germany

Dynamic advances in medical laboratory practices and diagnostic abilities demonstrate the absolute need for hospitals to keep abreast of clinical developments as well as upgrade their laboratory facilities, devices and human resources. Thus European Hospital increasingly focuses on laboratory news and opinions. In this issue, in the lead up to the international LABMED Forum, we provide a taste of stimulating trends and ideas.

POCT – clinical application, IT and technology

Moving towards deeper diagnostics

Just two decades ago, even though promising, point-of-care testing (POCT) was only used in hospitals and surgeries by a small number of specialists. Today POCT is in use throughout healthcare. During the third POCT-Symposium initiated and directed by Professor Peter B. Luppa, from Rechts der Isar Hospital, at Munich's Technical University, EH asked him to forecast developments within the next decade.

Looking to the future, Professor Peter Luppa said: 'One clear trend is infectiology and, above all, molecular diagnostics for infectious agents. Another major topic, already intensively discussed, is the continuous measurement of metabolites. This not only includes glucose but also other parameters that must be continuously monitored on the intensive care ward.'

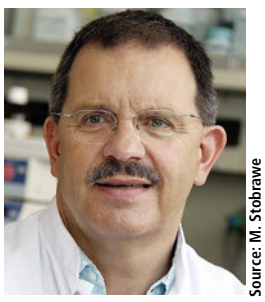
The Munich symposium focused on nine subjects, which included point of care management for chronic diseases, and POCT in Developing Countries. 'Technical' topics included advanced POCT technologies and applications, and Regulations and norms for POCT equipment. Is there a trend here?

'The most important topic is clinical application. IT is important during the implementation of the clinical applications. Vice versa, we need the IT regulations to improve the availability of POCT for the users. The regulatory aspect is therefore very important so that the developers can assess what's possible; not everything that's being developed can be used immediately for patients.'

Does this mean that new devices, procedures, solutions etc. should be developed in cooperation with the respective industries?

'Yes. Any developments within the medical devices industry should occur in close cooperation, synchronously, so to speak, with the users, to verify the advantages of the technology and procedures. It is essential that the benefits and outcome for patients are taken into consideration and are clearly evident.'

The two previous symposia (2012, 2014) were predominantly German events. This year saw greater internationalism – languages were German as well as English, over three days, speakers from nine different countries held lectures, and the exhibition was also international. During the symposium, it became apparent that two speakers, Dr H. Stekel, from Linz in Austria,



Source: M. Stobrawe

Professor Peter B. Luppa is head of the Central Laboratory and Blood Bank at the Rechts der Isar Hospital in Munich's Technical University in Germany. His main scientific interest lies in the regulation of steroid metabolism and biosensorics, aiming to develop improved analytical-diagnostic procedures for autoimmune diseases. From this, POCT in the hospital developed as a further focus. He has published more than 125 contributions in international journals and is a co-editor of the first German specialist book on point-of-care Testing (now in its 3rd edition).

Continued on page 22

'We must act now – or we may run out of options'

Antibiotics don't generate large profits

During our European Hospital interview with specialist in microbiology, virology and infection epidemiology Beniam Ghebremedhin MD, from the University Hospital Wuppertal, spoke about the impact of migration on infections, and ways to tackle the problem of multiresistant pathogens

'There is a lack of specialists in infectious diseases, for direct patient care on hospital wards as well as in the field of infectiology and diagnostics,' infections specialist Dr Beniam Ghebremedhin agreed. 'We are also short of specialists in infection prevention and control, along with microbiologists and virologists. In these times of multiresistant bacteria and large-scale microbial infections we should be promoting and supporting a new generation of specialists to strengthen research and diagnostics.'

This June, the EU published guidelines on dealing with antibiotics to help contain the spread of resistance. Could this help?

'The topic is of great importance as there are still many areas where anti-infectives are prescribed too quickly and not in a targeted manner. Due to time constraints in outpatient care for instance, antibiotics are often prescribed so that patients can be treated as quickly as possible. However, Amoxycillin or Cefuroxim are the wrong drugs to treat viral infections. There should be much more emphasis on treating patients with more precision, and on adapting treatment to their individual risk factors.

'Apart from the EU guidelines, there are already other recommendations on how adequate treatment should commence, such as the "Tarragona Strategy". This is the basic concept for adequate, initial treatment of bacterial infections with antibiotics. It includes the recommendation that the patient should receive a systematic examination if there is a lack of relevant information, such as where the patient is from and their local epidemiology (frequency of infections and resistance), because appropriate treatment cannot be given when these factors are not known. The focus should be on the dose, length of treatment and monitoring, along with the severity of the disease, all of which also requires as much information as possible about the patient. It is critical for the prognosis that adequate treatment commences without delay and with a high dose.'

In Germany, there is no specific training programme for doctors wishing to qualify in infectious disease treatments. However, additional qualifications can be obtained. Once someone has qualified as a specialist registrar and worked in infectiology for at least three years they can obtain a Certificate for Infectiology DGI, after attending the respective course. The lack of a specific area and course of studies for infectious diseases is a German particularity. The EU, including England, along with Switzerland and the USA all have respective training programmes in this field.

At Medica 2017 you will focus on 'Infectiology – New Multiresistance in Times of Migration'. Why?

'Viruses and bacteria know no borders. Worldwide migration is very much on the increase, not only as waves of refugees but also because of open borders and changes in travel habits. Holidays abroad and working on different continents have become the norm. However, this also means that locally occurring infections no longer remain local.

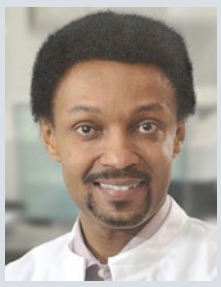
A pathogen such as an influenza virus can quickly spread globally. Bacteria are carried from one country to another in suitcases. If we want to treat patients correctly we therefore need to know where they are from, which pathogens they could have brought with them, or which multi-resistant pathogens they may have been exposed to.

'This is of particular importance in the case of multiresistant pathogens. In my lecture, I will talk about gram-negative bacteria such as Escherichia coli, Klebsiella pneumoniae or Acinetobacter baumannii, all of which have taken on greater significance. The latter in particular has made the headlines, in Kiel for instance and in Stuttgart at the beginning of this year.'

What can be done against multiresistant pathogens?

'This is a very important and also difficult question. Germany must definitely improve its procedures for infection prevention and detection. Infected patients need to be isolated earlier. In the Netherlands, the isolation of risk patients on admission is standard practice, in Germany; however, the capacities for isolation procedures are often insufficient. This is a strong point of criticism, as things are getting serious: the last weapons we can utilise in the fight against multiresistant pathogens are becoming ever blunter.

New anti-infectives are rarely approved and only have specific effects. Around thirty new substances are currently being examined in studies, but only four or five of those are likely to make it to the market. However, rather than multi-purpose weapons, these will be substances working against very specific pathogens only. Furthermore, resistance is developing much more quickly now. Where some substances used to be effective for up to ten years, this is now wishful thinking.'



Beniam Ghebremedhin MD PD will discuss 'Infectiology – New Multiresistance in Times of Migration' at the Medica Labmed Forum 2017, on 16 November 2017 in Düsseldorf, Germany. The free discussions will normally take place between 11am and 4pm in the new exhibition Hall 18, Conference language: English.

Is the pharmaceutical industry active in this area?

'Not as much as we'd like it to be; unlike cancer drugs, antibiotics don't generate large profits. Investment in studies is expensive, and treatment with antibiotics is not always comprehensive enough to regain the money invested.'

Another major problem: violation of hospital guidelines on infection prevention and control.

'Correct – and hand hygiene is critical here. This could help avoid a third of all transmissions of pathogens. Many places now have specially trained nurses who work in this field. Unfortunately, they have to fight obstinate colleagues on a daily basis. However, hygiene knows no hierarchy and a bacterium is not interested in chains of command. We must act now – otherwise we may well run out of options in the fight against multiresistance.'

Moving towards deeper diagnostics

Continued from page 21

and Dr R. Fried, from Zurich, Switzerland, spoke about national issues when it came to regulatory requirements for POCT. Their respective contributions were entitled requirements for POCT in Switzerland, and ISO 22870 in Austrian Practice. Is there still considerable work to do in Europe on the development of unified standards, definitions and values etc.?

'Some European guidelines exist already. For example, the ISO 22870 is now not only used in all European countries but also worldwide. However, when it comes to the respective translation and implementation into national laws there can be inconsistencies. This is why we took a closer look at these two countries. We saw that the ring trials carried out for quality assurance, for instance, are organised on a national level, i.e. EU law is being converted into national law. In some other countries, such as France, we can see that the conversion is organised in a different way.

Is there European or international cooperation, for example working groups, commissions, or committees?

'There are many active European and international committees in this field. It has become apparent that the Asian region needs to reposition itself, and we are working intensively on this. In the past, Asia has almost exclusively aligned itself with the FDA, based on the motto that whatever they approve automatically becomes licensed in Asia. But there has been a change here recently: both India and China, for instance, have now also developed analogue and national systems.

'International cooperation is in good shape. The ISO norms are an excellent example here as, once they have been introduced, a country cannot really opt out again. However, the application is not compulsory, which means that national requirements can still be considered. In any case, it's beneficial that ISO norms are now used as a foundation worldwide. 'This trend is reinforced by the fact that the industry, which revolves only around a small number of manufacturers here, is not interested in national solo efforts.'

Courtesy of EKF

When the medical trade show Medica takes place in a few months' time, Professor Georg Hoffmann, from Trillium Verlag, will hold a four-day 'LabMed Forum Medica'. On 15 November you will preside over the topic 'From self-test to continuous glucose monitoring'. Will this focus exclusively on POCT for diabetes?

'Obviously the focus will be on diabetology, but we are not limiting ourselves and can also accommodate the interests of our participants. The event will be held for the first time and we are curious about how it will develop. Previously at Medica several working groups and symposia focused on POCT, when diagnostics still played an important part at this Düsseldorf-based event. That's why we will now observe developments and draw our conclusions.

'So, this time, we will mainly focus on continuous glucose monitoring. For other parameters that can be continuously monitored, such as lactate or other cardiac markers, the applications are still more straightforward.'

'We are ticking

Multidrug-resistant organisms (MDRO) are keeping infection specialists worldwide on their toes. One of these specialists travelled all the way from Leipzig to India to gain insights in one of the sources of the problem.

Report: Katrin Schreiter

Dr Christoph Lübbert, infection specialist at University Hospital Leipzig, Germany, is deeply concerned about the global risk multidrug-resistant bacteria are causing – well knowing that the problem is anything but new. Between 2010 and 2013, his very institution, Leipzig University Hospital, suffered, up to then, the largest known and highly alarming outbreak of KPC (Klebsiella pneumoniae carbapenemase-producing bacteria) in Germany.

A fatal chain of events

A 66-year-old male patient had been transferred from a hospital on the Greek island of Rhodes to University Hospital Leipzig. The patient, who needed mechanic ventilation, was initially admitted to the hospital's ICU. Later, he was moved to a general ward, at a point when the exact type of pathogen the patient had acquired abroad was not yet microbiologically determined. The situation spiralled out of control: in the ensuing months patients primarily at the interdisciplinary surgical ICU were diagnosed with infections.

Spreading of the pathogen, from patient to patient, most likely via staff hands and exacerbated by contaminated surfaces, is thought to be the most likely cause of the extended outbreak, which was only stopped after an internal task force strictly enforced a combat strategy. The commonly used antibiotics did not yield the desired results; in short, the most effective weapon in the fight against this pathogen had turned blunt. Forty-two of the 100+ infected, mostly severely ill patients died, seven of them most likely as a direct consequence of the KPC infection.

'Back then we saw what happens when all of a sudden certain antibiotics don't work any more – and we learnt how decisively we have

Journalist Christine Adelhardt, conservationist Anil Dayakar, infectiologist Christoph Lübbert and cinematographer Tilo Gummel take samples in a lake in an industrial area of Hyderabad

e sitting on a time bomb'

to react in such a situation,' says Dr Christoph Lübbert who since then has focused his clinical research on multi-drug-resistant bacteria and considers University Hospital Leipzig to be well prepared for infection outbreaks.

A few months ago, the 46-year-old physician joined a team of investigative journalists from different German media on a trip to Hyderabad in India to examine industrial wastewater near large pharmaceutical companies that provide the most important antibiotics for the global market.

Eighty to 90 percent of all antibiotics are being produced in India and China. 'In more than 95 percent of the samples taken at a total of 28 sites we found multidrug-resistant bacteria with important resistance mechanisms such as ESBL or carbapenemase-production,' Dr Lübbert explains and adds that 'Almost all environmental samples taken at a total of 16 sites contained relevant levels of antibiotics and antimycotics.'

A sample from a drainage ditch in the industrial district of Patancheru-Bollaram contained 237 mg/l of the antifungal substance fluconazole. 'This is 20 times more than the maximum level allowed in the blood of severely ill patients,' Lübbert reports and points out that this is 'the highest level of a pharmaceutical that has been detected in the environment – ever.' 'In India antibiotics abuse – in human as well as in veterinary medicine – is widespread' according to Dr Lübbert, 'There are already many resistant pathogens – but if on top of that antibiotics are released into the environment we are making a ticking time bomb even deadlier: we create multidrug resistances.'

For some infections acquired in India there is no effective therapy any more. 'Basically no antibiotic will work,' the physician noted. One study found that in India every year 60,000 new-borns die of MRD bacteria.

This problem is not going to be limited to India. 'No matter where new resistances develop, they travel fast due to patients, food stuff and travellers moving around – and due to migrant birds.'

For Lübbert this is a global issue, which requires a global action plan: 'When we procure pharmaceuticals from emerging countries we have to have independent auditors check whether the environment is being contaminated.' This kind of transparency, the expert says, is currently not being provided since pharmaceutical companies can continue to obfuscate production conditions. It seems, Dr Lübbert conjectures, that financial yield takes priority over collateral damages such as destroyed environment. 'We have to react, and if push comes to shove we have to be able to close the European market for products that were manufactured under questionable conditions.'

'At the same time we need new and better antibiotics,' Lübbert urges, taking the pharmaceutical industry to task. But he knows that pharmaceutical research and development is a slow process: 'It usually takes 10 to 15 years from the lab to approval.'

While in Germany the situation is far from being as bad as in India, things have to change here as well, Lübbert warns. 'We have to make sure that antibiotics are not being released in the environment – and that they are not being used indiscriminately. Many physicians are much too quick to prescribe antibiotics, and this also holds true for veterinarians, particularly in the field of industrialised livestock production.'

These practices have serious consequences. 'As soon as bacteria are put under evolutionary pressure by antibiotics, they form resistances.' Today, there are two or three antibiotics that are effective against extremely multi-drug resistant organisms – not enough. 'We are running out of time,' Lübbert says and adds he hopes that the G20 summit in Hamburg, where India as well as China will be represented, will yield results. National antibiotics action plans are on the summit agenda as well as transparency in pharmaceutical production and guidelines for physicians and veterinarians

Biology and medicine graduate Christoph Lübbert MD PhD is currently Director of the Department of Infection Medicine and Tropical Medicine at Leipzig University Hospital in Germany. In 2016, he received the Internal Medicine Prevention Award from the German Society for Internal Medicine (DGIM).

©PHOENIX/N.DR/Christoph Bluhm

Going international – the only way to win

Combating CRAB and carbapenem resistant bacteria

Antimicrobial resistance mortality is set to surpass cancer and traffic-related deaths by 2050, according to the UK National Health Service (NHS). Carbapenem-resistant Acinetobacter (CRAB) and carbapenem resistant Enterobacteriaceae, two of the most common bacteria involved in these types of infections, are the object of the COMBACTE-CARE's EUropean prospective cohort study on Enterobacteriaceae showing REsistance to CArbapenems (EURECA). European Hospital asked Belén Gutiérrez-Gutiérrez, coordinator of the project, how it will improve knowledge of risk and prognosis factors, and what is the best available treatment.

Report: Melisande Rouger

'According to a report published by the UK National Health Service (NHS) in 2016, antimicrobial resistance mortality will increase from the current 700,000 to 10 million annual deaths by 2050 – unless extraordinary steps are taken to control it,' Belén Gutiérrez-Gutiérrez pointed out. 'To give an idea, 10 million deaths per year are more than the current number of cancer or traffic-related deaths.

UN declaration acknowledges the gravity

'The United Nations member states also signed a declaration acknowledging the gravity of drug resistant bacteria.

'Carbapenem-resistant gram-negative bacteria Acinetobacter baumannii, carbapenem-resistant Pseudomonas-aeruginosa, and carbapenem and 3rd generation cephalosporin-resistant have been defined as first priorities by the WHO in its list of antibiotic resistant bacteria that are a risk to human health.'

Currently 53 hospitals in ten countries take part in the study, with 836 patients enrolled – so 40% of the total estimate. These patients will serve to improve knowledge of risk and prognosis factors, and best available treatment in infections due to CRAB and carbapenem resistant Enterobacteriaceae. They will also serve as a historical comparative cohort for new clinical trials to develop new antibiotics.

First results to be aired at ECCMID 2018

'The study will close by February 2018 and we hope to communicate our first results during the European Congress of Clinical Microbiology and Infectious Diseases (ECCMID), which will take place in Madrid in April next year.'

'First, we must raise public awareness of increasing antibiotic resistance and its relationship with antibiotic overuse. It's key is to raise not only public awareness but also among HC professionals and the pharmaceutical industry of how important it is not to abuse antibiotics and use them only when strictly necessary.

'Then we must analyse how these microorganisms are transferred and prevent them in the hospital and the community.

'We must also reduce the unnecessary use of antibiotics in animals for human purposes, and promote new diagnostic tools to early detect infection and reduce the unnecessary use of antibiotics when there is no infection.

'Last but not least, we must develop new antibiotics and optimise antibiotics that are already available.'

How the coordination role began

'We had just finished including cases from INCREMENT, another international observational study on bloodstream infections (BSIs) due to extended spectrum β-lactamase-producing Enterobacteriaceae (ESBL) and/ or carbapenemase-producing Enterobacteriaceae, when Dr Jesús Rodriguez-Baño, who leads the EURECA study, asked me to coordinate it. I am part of a great local team of seven professionals, who help me coordinate and manage the study together with the COMBACTE Clin-Net, Stat-Net and Lab-Net networks.

Other research projects

Until recently I was coordinating the INCREMENT project. Now I'm coordinating INCREMENT-SOT, a study in transplanted patients with BSIS due to extended spectrum β-lactamase-producing Enterobactamase (ESBL) or carbapenemase-producing Enterobacteriaceae, together with Reina Sofia Hospital in Cordoba and 12 October Hospital in Madrid.

'I am also part of the research team in another international project, the MODERN study, on ESBL transmission and epidemiology.'

Facing the challenges of drug resistant bacteria

'At the Infectious Diseases and Clinical Microbiology Unit in Virgen Macarena University Hospital, in Seville, we have a team of specialists who are responsible for controlling and managing patients with nosocomial infection. Multidisciplinary work, joining infectious diseases physicians, microbiologists, nurses, pharmacists and preventive medicine specialists, is essential for these patients. We need to diagnose the infection due to a drug resistant bacteria early, to treat it with the best available therapy, and to rigorously manage treatment to guarantee a successful outcome. Also, it's key to take isolation measures and develop antimicrobial stewardship.'

A specialist in internal medicine, **Belén Gutiérrez-Gutiérrez MD** works in the Infectious Diseases and Clinical Microbiology Unit at Virgen Macarena University Hospital, Seville, Spain. Gaining her PhD at Seville University and a degree in epidemiology and clinical research from the University of Granada, today she is involved in various international antimicrobial resistance research projects.

The importance of a multidisciplinary international network

'In our daily work as infectious diseases physicians, we increasingly have to manage patients with infection due to bacteria resisting almost any type of antibiotics. You realise how necessary and important it is to have a multidisciplinary and international network such as COMBACTE. Our objective is to work all together in the same direction to fight these infections.'

EURECA is a prospective observational study within the COMBACTE-CARE project, which is promoted by the Innovative Medicines Initiative (IMI), a consortium between the EU and the European Federation of Pharmaceutical Industry Associations (EFPIA). The project focuses on combating carbapenem-resistant Gram-negative bacteria.

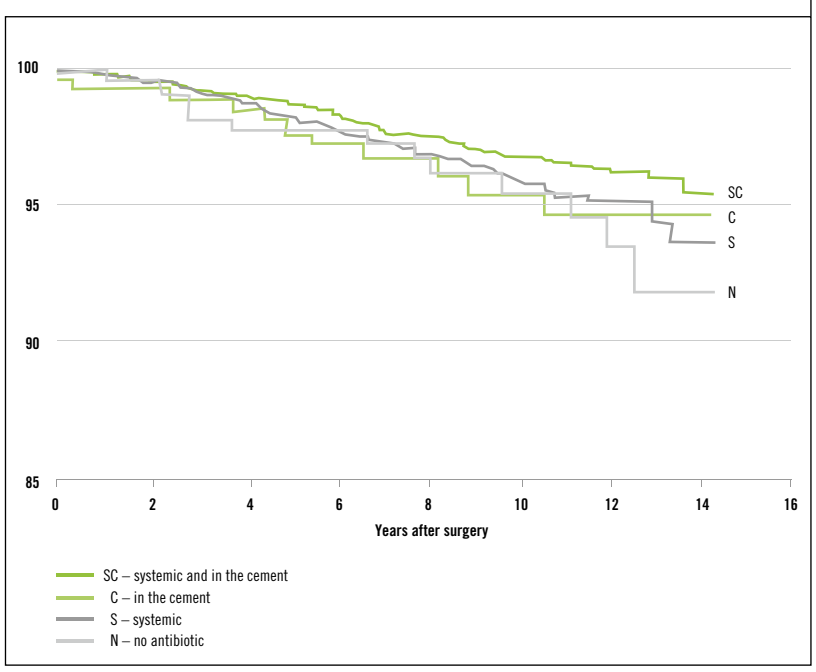
Effective prophylaxis beats the best treatment

Antibiotic-loaded bone cement cuts costs

Antibiotic-loaded bone cement is a cost-efficient periprosthetic joint infection prophylaxis after knee and hip joint arthroplasty.

Periprosthetic joint infection (PJI) is a dreaded post-surgical complication occurring in one to three percent of knee and hip joint arthroplasties. 'With PJI, the five-year survival rate is significantly lower than for testicular cancer, Hodgkin lymphoma, melanoma and breast cancer,' explained Nils P Hailer, Professor of Orthopaedics at the Department of Surgical Sciences/ Orthopaedics at Uppsala University Hospital, Sweden.

'The good news: there is an effective prophylaxis,' the expert told delegates at the 18th EFORT Congress (Vienna. 31 May - 2 June) 2017, during a satellite symposium on antibiotic-loaded bone cement (ALBC) organised by Heraeus Medical, a German medical device manufacturer.



Norwegian Hip Registry: Revision risk is lowest if systemic and local antibiotic prophylaxis are combined

PJI is caused by biofilms forming on the implant surface. 'It takes very few – only about 200 – bacteria to trigger the biofilm,' said Dr Andrej Trampuz, Head of the Infectious Diseases Research Laboratory at Charité Medical University in Berlin, Germany.

In acute infections (< three weeks), retention of the prosthesis is the treatment of choice. However, in chronic infections, exchange of the prosthesis is crucial to achieve high treatment success, Trampuz added. 'A mature biofilm – older than three weeks – is impossible to eradicate without implant removal.'

Infection is the best possible complication

'To achieve high treatment success, a concerted surgical and antimicrobial concept is needed,' Trampuz emphasised. Such a planned approach can indeed achieve success rates of over 90 percent. Even further, he said: 'Infection is the best possible complication, if appropriate diagnosis is combined with correct surgery and efficient anti-biofilm agents.'

The basic principle of any therapy is to select the least invasive treatment option depending on the present features with the best functional result. Guidance is provided by the recently updated Pocket Guide to Diagnosis & Treatment of Periprosthetic Joint Infection (PJI) published by the Pro-Implant Foundation (www.pro-implant-foundation.org).

Effective prophylaxis beats the greatest treatment

Many studies involving different methodologies support the use of single dose antibiotic-loaded bone cement to reduce the risk of infection after knee and hip arthroplasty.

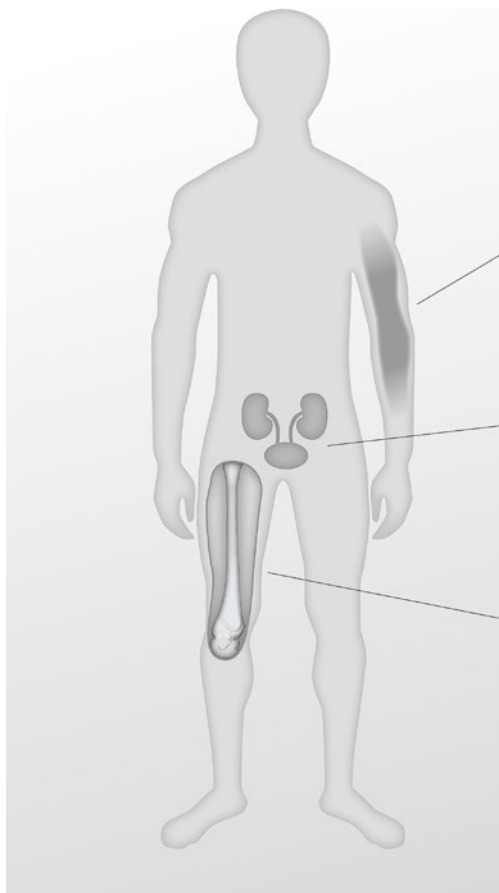
A Spanish study shows that the introduction of antibiotic-loaded bone cement (ALBC) Palacos R+G in knee and hip joint procedures in Spain in 2011 lowered PJI rates by 72% in hip procedures and 60% in knee procedures (including arthroplasty and fractures).

Despite these data, there are still some European countries where ALBC is not used due to additional costs of $200-500 compared to plain bone cement.

If those one-off costs are compared to the costs generated by PJI, consistent use of ALBC is significantly cheaper: according to the Spanish study cost reductions of €2,672 per patient receiving hip procedure were realised.

Dual ALBC proves effective in hip hemiarthroplasty

In the treatment of high risk patients with intracapsular neck of femur fractures, dual impregnated bone cement (Copal G+C) has proven to reduce infection rates for deep surgical site infections (SSI) by 68%, according to Professor Mike R Reed, consultant trauma and orthopaedic surgeon at Northumbria NHS Trust,



Concentration of local and systemic antibiotics. If applied locally up to a thousandfold higher concentration is possible

Interdisciplinary and international cooperation is vital

The global need for virologists

Over recent years, virology, once medicine's step-child, moved into the limelight, pushed by impressive progress and pulled by globalisation-induced need for expertise in virus diagnostics and viral epidemics. In the run-up to the annual congress of the European Society for Clinical Virology (ESCV) in Stresa, Italy (September 2017), EH spoke with past ESCV president Professor Elisabeth Puchhammer-Stöckl, deputy director of the virology department at Vienna's Medical University.

Report: Walter Depner

Asked how the clinical virologist job description has changed over recent years, Professor Elisabeth Puchhammer-Stöckl, from Vienna's Medical University, agreed that this has indeed changed. 'During the past decade or so, many new diagnostic tests were developed and many viruses were identified. Thus we have much more complex tools today to detect viral infections. Qualified experts in virology and virus diagnostics are important for patient management in a hospital setting.

'With an increasing number of very good therapies for certain viral infections antiviral resistance is gaining importance. Today, virologists need in-depth microbiology knowledge. In view of the increasing mobility of people worldwide we also have to be familiar with viral epidemics across the globe and we need a tight global network.'

Do you already know which top topics will be at the ESCV congress, or will you decide depending on developments, such as the avian flu virus?

'At congress we usually deal with certain topics in clinical virology that are always important, such as respiratory viral infections or viral infections in immunocompromised patients. In addition, we always include current issues and invite experts at short notice. That will be the case in Stresa.'

What results do you expect from this event?

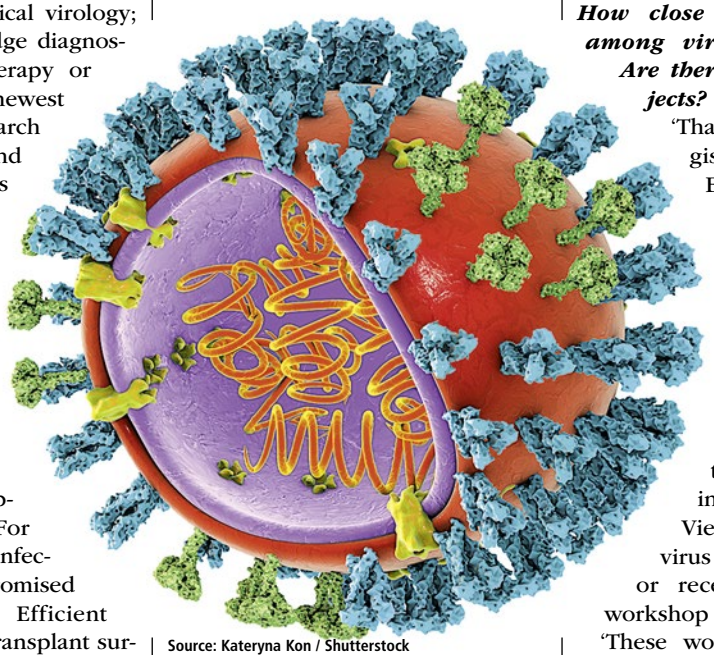
'The congress will offer international training for clinical virology; it will cover cutting edge diagnostics, epidemiology, therapy or vaccinology, and the newest results in basic research will be presented – and obviously the congress is an important networking forum for the colleagues.'

In healthcare 'interdisciplinarity' is increasingly important. What does that mean for virology today?

'Interdisciplinary cooperation is crucial. For example, take viral infections in immunocompromised transplant patients. Efficient cooperation between transplant surgeons, internal medicine specialists, microbiologists and virologist is essential for the patient's long-term survival. But cooperation with paediatricians or gynaecologists, for example, is equally important.'

The same holds true for globalisation. An isolated country loses relevance. How important is international cooperation in your discipline?

'Globalisation facilitates international networks – and they are very important in virology. Rapid dissemination of news and data on epidemics across our network, international cooperation with regard to the identification and analysis of viruses, joint efforts to combat viral infections – all this is invaluable. As we have seen in the cases of SARS, it is highly successful.'



Source: Kateryna Kon / Shutterstock

From a virologist's viewpoint, should mobility be restricted or changed; and if so, how?

'I don't think so. Travellers should be comprehensively informed about the infection risk in their destination. Competent travel information and targeted risk assessment for the individual traveller are desirable.'

How close is the cooperation among virologists in Europe? Are there joint research projects?

'Thanks to ESCV, virologists cooperate closely. ESCV not only organises the annual meetings but it also organises and funds specific workshops throughout Europe. We conducted a very successful workshop in Regensburg on congenital viral infections, on new methods in virus diagnostics in Vienna and Istanbul, on virus serology in Trondheim or recently the enterovirus workshop in Oxford.

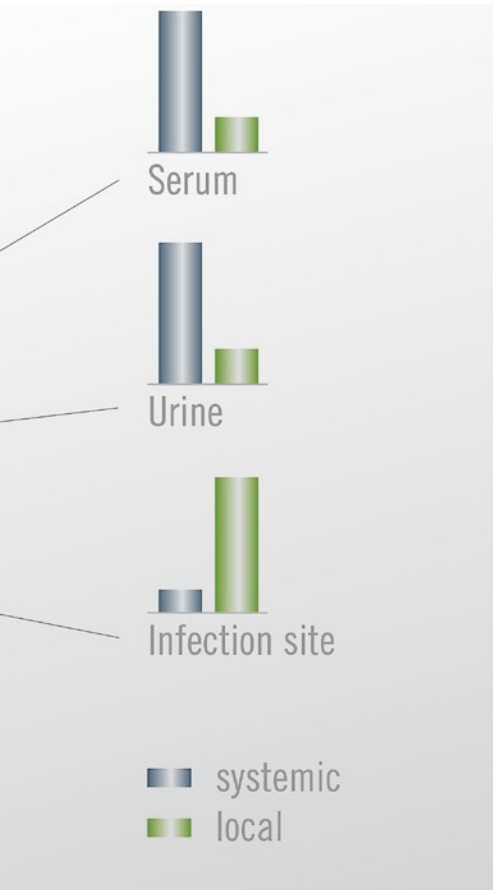
'These workshops are primarily open to ESCV members and only a small fee is charged. The small participant groups have two days to look intensively into a certain topic, with experts on their side. There is time to discuss basics as well as clinical and diagnostic guidelines, clinical case studies are presented and the virologists have the opportunity to network in an amicable environment. 'We have our first workshop soon on viral infections in transplant patients scheduled in St Petersburg and we hope to be able to encourage our Russian colleagues to join the European network.'

Professor Elisabeth Puchhammer-Stöckl is deputy director of the Department of Virology at Vienna's Medical University in Austria where she, inter alia, heads research teams focusing on viral infection in immunocompromised patients; development of viral resistance against antiviral therapies and the development of new methods in virus diagnostics. The professor is a member of several European scientific committees and on the peer review board of several international journals and EU projects.

Today, Europe is a small part of the globalised world – which means international cooperation must intensify. Does this work well?

'There are numerous global networks. We European virologists have a sister association, the Pan-American Society of Clinical Virology, with which we are in constant exchange.

'Moreover the virologists have international networks of their individual specialisations such as HIV, hepatitis or herpes viruses.'



Newcastle University, and one of the authors in a randomised clinical study.

Despite the higher antibiotic dose, no adverse effects, such as an increase in Clostridium difficile infections or renal impairment, were recorded. Reed concluded: 'High-dose dual antibiotic cement in hip hemiarthroplasty reduces deep infection rates, does not drive antibiotic resistance and is cost effective.'

New POCT gastroenteritis testing

Norovirus identification speeds up

Norovirus, the most common cause of gastroenteritis in humans, affects people of all ages. Norovirus diagnostics is based primarily on electron microscopy and molecular biological techniques. However, using electron microscopy to visualise the virus particles in stool specimens is insensitive. Additionally, antigen-ELISAs are less sensitive and can result in many false negatives. Real-Time PCR assays have been developed to detect Norovirus GI and GII in faecal patient samples. This current gold standard method shows the best performance data, Biomed Labordiagnostik GmbH points out. 'The GenomEra Norovirus assay is a qualitative in vitro diagnostic (IVD) nucleic acid test intended to detect and differentiate Norovirus GI and GII from raw or unpreserved, unformed stool specimens,' the company reports. Further itemising the system's assets, Biomed states: The test is for low and middle throughput, running four samples in parallel. The irreversibly sealed test chips are preloaded and ready-to-use. A processing control ensures the correct sample preparation and functions as an amplification control to monitor assay inhibition.

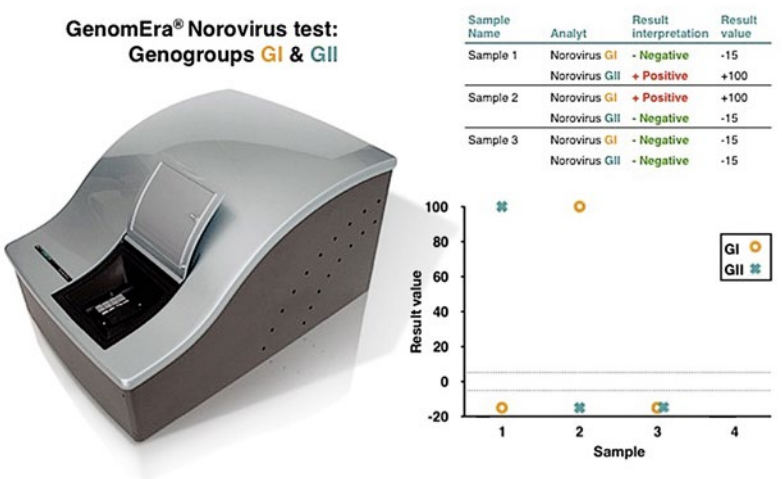
The turnaround time is 80 minutes maximum, with automated result interpretation and reporting.

The highly stable fluorescent lanthanide reporters prove a unique combination, Biomed adds.

'This is proprietary time-resolved detection technology.'

This test can be easily performed on demand on the GenomEra CDX Instrument (Abacus Diagnostica, Finland). 'The GenomEra Norovirus RT-PCR assay is intended to aid diagnosis of norovirus infections when used in conjunction with clinical evaluation, laboratory findings and epidemiological information and in the context of outbreaks,' Biomed points out

Further details: www.biomed.de



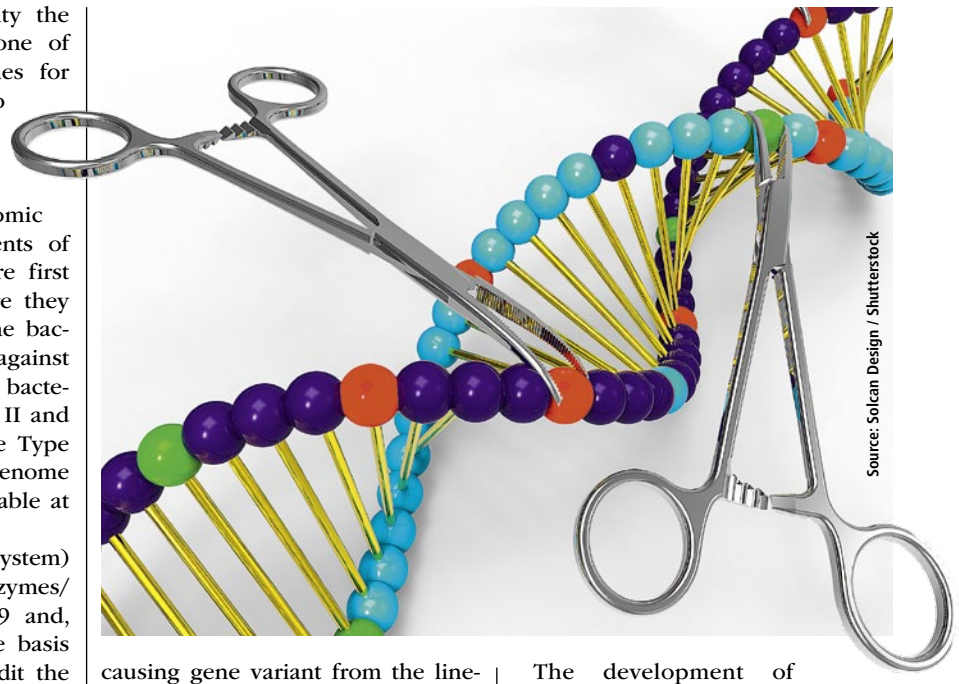
CRISPR/Cas9 and Sherlock

Savers, healers or threats to life?

Report: M van de Wouw

Modifying a DNA sequence to alter a cell to cure a disorder, prevent a genetic disease being passed on to next generations, or to use genetic modification as a way to diagnose a virus: yes, these tasks are possible. The recently discovered CRISPR technique can do it all.

Already in 1987 researcher Yoshizumi Ishino, at Osaka University, described the possibility of genome editing. In 2012-2013 scientists discovered genetic modification of a specific DNA sequence in a cell and gave it the name CRISPR. The discovery was runner up in 2012 and 2013 in Science Magazine's Breakthrough of the Year award. CRISPR won the award eventually in 2015. Largely due to its simplicity and adaptability the technique rapidly became one of the most popular approaches for genome engineering. And so the development goes on.


Source: Solcan Design / Shutterstock

CRISPR is - an abbreviation of Clustered Regularly Interspaced Short Palindromic Repeats. These short segments of repeated codes in DNA were first discovered in bacteria, where they play a key roll as part of the bacterial defence mechanism against viruses. So far, three distinct bacterial CRISPR systems, types I, II and III have been identified. The Type II system is the basis for genome engineering technology available at this moment.

Cas (CRISPR Associated System) is the name for different enzymes/proteins. Cas 9 is protein 9 and, together with CRISPR, is the basis for the technique used to edit the human genome. Cas9 is programmable and works in any type of cell.

How it works - CRISPR/Cas9 allows permanent modification of genes within organisms, therefore manipulating the code of life. It works like a pair of molecular scissors: when CRISPR is used to edit genes in a cell, a small strip of RNA directs an enzyme capable of cutting DNA at a desired location within a genome. This allows existing genes to be removed and/or new ones added. The cell recognises the damage done by the cut and 'glues' the pieces back together. And, although the cell is a bit shorter after the cut, it functions again.

Genome editing techniques have many potential applications, such as to target virulence factors, genes encoding antibiotic resistance, cancer, inflammation, foetal haemoglobin and even eradicate viral DNA in the case of Epstein-Barr virus (EBV). There are more than 3,000 genetic diseases, such as colour blindness or Huntington's disease, caused by one wrongly placed nucleotide in the DNA.

CRISPR may even revive the concept of transplanting animal organs into humans. The biggest problems in transplant rejection are the retroviruses present in animal genomes. Researchers are working on eliminating those retroviruses DNA.

Ethical issues - OHSU scientists recently used CRISPR on a human embryo to correct a mutation in nuclear DNA that causes a common genetic heart disease, leading to sudden cardiac death and heart failure. By removing the disease-causing gene variant from the lineage, every future generation would carry the repair. It was a success.

However, the potential to alter DNA in human cells needs more investigation, because it is still unknown what the long-term side effects will be. In future, potentially infected diseases may occur.

The use on human embryos also causes an ethical issue. How far should we go? Policy regulations for the CRISPR/cas9 system vary internationally. Researchers in China, Sweden and the United Kingdom are allowed to use human embryos for CRISPR interventions, although in the UK it is forbidden to implant the embryos. They must be destroyed after seven days. The Netherlands does not permit the use of human embryos.

According to some, the potential danger in the long run is the temptation to treat children not only for genetic disorders but also to make them perfect: superior intelligence, better eyes, and better muscles. Rules for applying CRISPR/Cas9 are therefore necessary.

Sherlock - Besides being able to repair DNA, CRISPR could soon also become a low-cost diagnostic tool to detect infectious diseases such as Zika or dengue. According to a recent article published in Science researchers have developed the Specific High-sensitivity Enzymatic Reporter (SHERLOCK), which stands for 'to make accurate, fast diagnoses'. This uses a different enzyme, Cas13a, which goes to RNA, rather than DNA. It chops through any RNA encountered and does not stop until that has gone.

The development of Sherlock gave medical laboratories a new diagnostic tool. And the scientific community is excited. Sherlock can detect pathogens in extremely small amounts of genetic matter and in an earlier stage. Besides that, tests can be performed using urine and/or saliva rather than blood. Quoted from Science: 'The detection sensitivity of the new CRISPR-Cas13a system for specific genetic material is one million times better than the most commonly used diagnostic technique'.

The technique is also highly portable, needs no refrigeration and costs as little as 61 cents per test in the field. Therefore Sherlock would be extremely useful in remote places without electricity or access to a diagnostic laboratory, providing clinicians the possibility to diagnose and treat illnesses.

CRISPR/Cas9 and Sherlock can change and save lives. Professor and Director Scott Weaver PhD, at the Institute for Human Infections and Immunity, University of Texas Medical Branch in Galveston, states in an article on Big Think: 'It looks like one significant step on the pathway that is the Holy Grail, which is developing point-of-care, or bedside detection, that doesn't require expensive equipment or even reliable power.'

Source: https://www.washingtonpost.com/news/speaking-of-science/wp/2015/12/01/historic-summit-on-gene-editing-and-designer-babies-convenes-in-washington/?utm_term=.765ca64aafaf
http://science.sciencemag.org/content/356/6336/438

Inspirational middlew

An intelligent blood sam

The sorting devices SortPro of the young German supplier ASP Lab Automation AG take over the collection and pre-sorting of the samples in the Accessioning area of clinical laboratories. The universally applicable devices, of which about 100 have been installed worldwide in the past 24 months, are characterised by high processing speed and easy operation.

As with comparable devices from other manufacturers, these have so far exclusively passed on the data they have collected to the laboratory information system (LIS) and received from there their commands to distribute the samples. With a new option package, for the first time, leading intelligence is used directly in the sorter and opens up new opportunities in the optimisation of the process sequences in the sample entry.

In July, ASP presented this middleware package to the public at the world's largest clinical chemistry conference, the American Association of Clinical Chemistry (AACC) in San Diego, California. This option package includes several features that improve handling in everyday operation and, in particular, a complete PC.

A greatly extended graphical user interface is running on a large touchscreen monitor. A special service tool counts every work step and determines any service requirement, which is displayed to the operator in time to arrange an appointment. Shortest standstill times with minimum service effort are thus realised.

The most important function, however, is the acquisition and evaluation of each individual sample processed by the device. The time course of the sample quantity, the frequency of individual requirements and other statistics can be called up in the extensive protocol function. The data

Point-of-care testing will enter many more medical sectors

New system beats the accuracy test

According to Marcel van Kasteel, CEO of Handheld Diagnostics at Philips, Point-of-care testing (POCT) has struggled with accuracy and thus its impact has been limited to certain sectors. However, Philips is confident that its Minicare system has overcome the issues, as Daniela Zimmermann's interview reveals

'What makes accuracy possible,' Marcel van Kasteel explains, 'is that Minicare I-20 has leveraged the power of magnetic nanobeads through Philips proprietary technology, Magnotech. This enabled us to create a next generation POCT system that specifically overcomes the problem of limited accuracy in those early models. Their magnetic properties are stable because they are not affected by reagent chemistry or other factors and that helps deliver assay quality and accuracy – and, importantly, stability so that clinicians have confidence that our system provides consistent, high quality results.

'Developing a troponin cardiac marker assay is particularly challenging, because sufficient sensitivity is needed at a picomolar level. The technology enables the Philips Minicare cTnI assay to provide clinical performance comparable to the highly sensitive lab tests.'

Marcel van Kasteel, CEO Handheld Diagnostics, joined Philips in September 2007. He has worked for 25 years in various roles within the In Vitro Diagnostics Industry, his last before joining Philips being Vice President for Diagnostics (EMEA and India) for Beckman Coulter in Switzerland. He has also chaired several committees in the European Diagnostics Manufacturing Association (EDMA).

Contributing to faster care

Using Minicare I-20 in accident and emergency (A&E) will deliver results on the spot, helping physicians towards quicker clinical decisions, van Kasteel points out. Rapid diagnosis can lead to faster treatment and results.

Alternatively, if POCT information helps an A&E clinician to rule out a heart attack quicker, then patients could be discharged sooner, and queues would ease.

In the pipeline

'Minicare BNP assay is the second IVD cardiac assay on the Minicare I -20 and is scheduled for launch Q4 2017. Again, it delivers results, at the patient's bed, within 10 minutes.

'Acute heart failure (AHF) – the most common cause of hospitalisation in over 65-year-olds – accounts for 5% of all emergency admissions in Europe and the USA. At the A&E, patients presenting with AHF need immediate treatment. However, once stabilised, non-acute HF can be treated by the primary care team. The A&E physician should be able to distinguish between both stages of the disease as quickly as possible. It provides the physician with access to a fast, accurate BNP marker test to help in the diagnosis of non-acute HF more quickly.

Philips has plans to further expand its range of emergency care markers with markers to measure traumatic brain injury, bacterial infection dyspnoea, to be introduced over the next few years.

Minicare cTnI as an ambulance asset

The potential for Minicare I-20 to be used earlier in patient care is especially exciting with benefits for patient outcomes and quality of paramedical service. We are already conducting several trials in Europe to support the use of Minicare cTnI by ambulance paramedics. It's suitable for them to use because it supports capillary samples. Also it's compact, robustly engineered, and easy to use.

Minicare C-300: up to 27 markers and 14 tests

'The ordering of those routine tests from the central lab usually takes 45-90 minutes before results are returned. With an extensive range of 27 chemistry parameters, the Minicare C-300 offers a busy department the chance to bypass this often time-consuming process. Having results ready in 15 minutes, at the point of care, aids in obtaining faster diagnosis in the A&E and faster subsequent admission of acute patients. The clinician potentially reduces a 30-75 minutes window of waiting time: invaluable in a fast moving department with constant time demands. 'Furthermore, it might allow A&E staff to discharge a patient earlier, with confidence.

'Although POCT for clinical chemistry is not widely used yet, its benefits are gradually being recognised by hospitals. The Minicare C-300 has specific benefits: a comprehensive menu suitable for disease management; unique reagent panels for acute care settings; lab comparable, high quality assays – and cost-effective.

Correlation with large laboratory systems

Philips Minicare C-300 has good correlation to the large core lab systems such as Roche Cobas and Beckman Coulter systems.

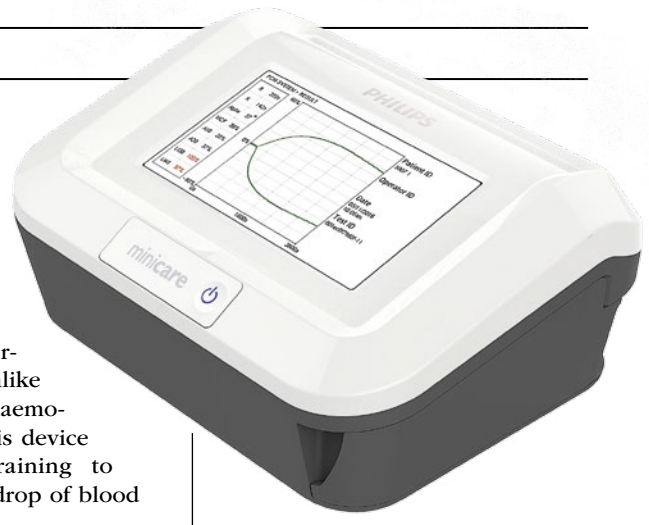
The system has a far more comprehensive menu including, for example, lipase, lactate and CRP, than is generally offered by POCT systems. In addition, a number of unique, customised clinical chemistry panels based on the direct feedback of European emergency teams are offered. The result, as said, is an analyser offering 27 individual parameters and customized reagent panels with up to 14 tests.

A novel coagulation system

'Knowing a patient's haemostatic function is a critical factor that determines patient outcomes in emergency or elective surgery. It's a technological innovation that underpins the performance of this compact, portable haemostasis system.

'Minicare H-300's unique ViscoGlass technology is the power delivering the precision of the visco elastic assay within this compact instrument. By sheer contact activation between two glass discs, Minicare H-300 assists trauma specialists and anaesthetists to assess the haemostatic status of critically ill patients within minutes, at the point-of-care – and receive full results within 15 minutes.

'The system has a small footprint and due to ViscoGlass technology no reagents are needed to perform the test. Unlike current complex haemostasis analysers, this device needs minimal training to use: simply add a drop of blood to the cartridge.'



are package efficiency

ple sorter

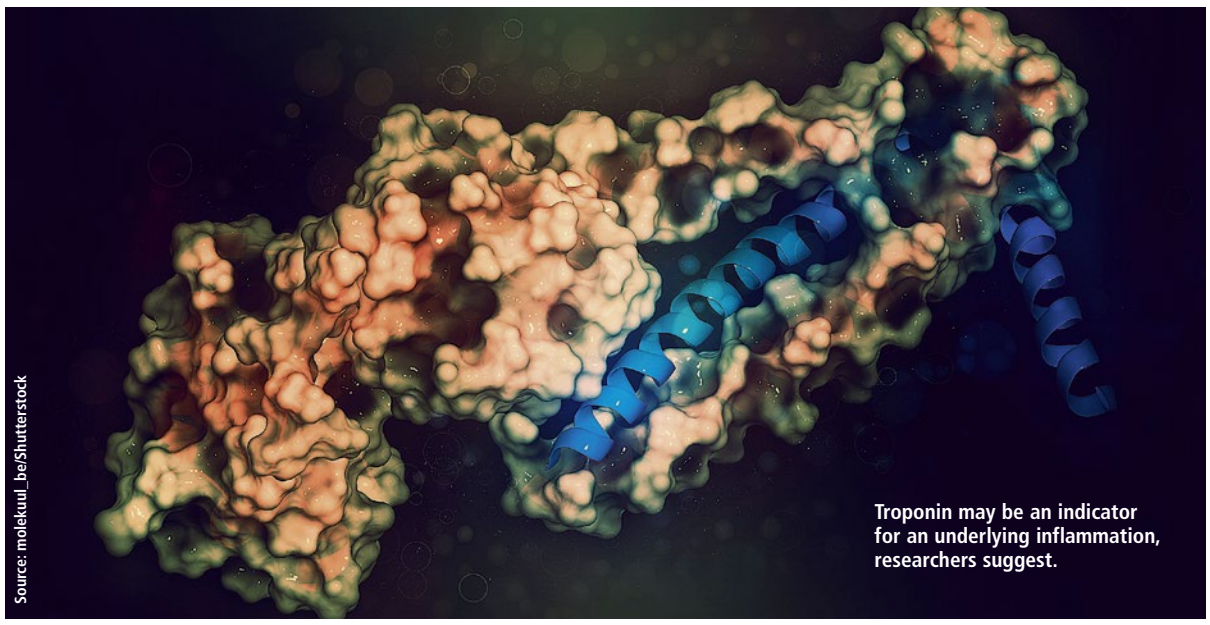
are also available for your own evaluations.

'The efficiency gains in the clinical lab, achievable with the middleware package, have inspired physicians from all over the world,' CEO Heino Pruess summarised regarding the response of a specialist audience at the US Congress. In Europe, the middleware package will be presented for the first time this October at the annual meeting of Deutsche Gesellschaft für Klinische Chemie und Laboratoriumsmedizin (DGKL 14), in Oldenburg, Germany.

Details: www.asplabauto.com

Blood test could help predict which patients survive surgery

High troponin levels yield a clue



Source: molekuul_be/Shutterstock

Troponin may be an indicator for an underlying inflammation, researchers suggest.

Report: Mark Nicholls

Researchers at the James Cook University Hospital, in Middlesbrough, UK, have developed a highly sensitive blood test that could be used before surgical operations to predict which patients are at risk of complications will survive in the long-term. Presenting their findings at the British Cardiovascular Society conference this June, they explained that they measured the level of troponin in blood samples taken from 993 patients before elective or emergency surgery. None of the patients had cardiac surgery.

The team found that 25% of the patients who had troponin levels of 50ng/l, or over, before their surgery died within six months, rising to 37% dying within 12 months of the operation.

In comparison, only 2.5% of patients with a pre-operative troponin level of less than 17ng/l died within six months. Only 3.7% of these patients died within a year of their operation.

The troponin test is routinely used in Accident and Emergency departments to diagnose a heart attack and measures blood levels of the molecule troponin, which is released into the blood stream when heart muscle is injured.

However, in this study 10% of patients had raised troponin levels without having suffered any previous cardiovascular events.

Dr Matthew Jackson, a Research Fellow at the James Cook University Hospital, emphasised that the study group of patients that were examined all came in for surgery at the hospital without being pre-selected for the research. 'That's how this study differs from previous studies in this area that looked at selected high-risk groups or people undergoing specific high-risk surgery,' Jackson added.

While the link between the raised troponin levels and an increased death rate after surgery remains unclear, the researchers suggest that a high troponin level may show that a person is suffering from underlying inflammation. To see whether inflammation could explain the increase in death rates, the researchers are now testing the blood samples for other signs of inflammation, such as raised inflammatory markers (C-reaction proteins).

Matthew Jackson MD is an interventional cardiology trainee and Research Fellow at James Cook University Hospital, Middlesborough, UK

The team hopes their work will lead to new ways to improve patients' survival after undergoing an operation. 'By helping us to better predict how patients will fare after surgery, this test may help doctors to identify patients who could benefit from additional tests and medication to get them ready for their surgery and more intensive monitoring as they recover after their operation,' Jackson said. 'Now we need to find out why troponin levels are raised in some patients before surgery, and why these patients are more likely to die, in order to identify treatments that could reduce the risk of death following non-cardiac surgery.'

Further studies are planned to repeat the data in a more prospective way and look at areas such as inflammation markers.

Blood test could help predict which patients survive surgery

A new generation of coagulation analysers

Teco Medical Instruments has produced coagulation analysers for a quarter of a century. Its new instrument line of manual and semi-automatic coagulation analysers – available in three versions, Coatron X Eco, Coatron X Pro and Coatron X Top, Coatron X – offer one, two and four channel optics and selected sample and reagent positions and, the firm points out, adding that the equipment provides the highest optical resolution; enlarged optic range; smallest sample and reagent volume 0,1 mOD – 3500 mOD, with 75µL sample and reagent volume, to provide a complete optical analysis. Additionally, no further parts, e.g. balls, or stirrers, are needed, Teco points out.

The light level adjustment of the optic channels for each sample is automatic. Stray light reduction, exact temperature control, all parameter are preset.

The internal barcode reader scans a patient's identification on the primary tube before measurement and this is combined with the result.

If the instrument is connected to a Laboratory Information System (LIS) or Tecam Software, the patient ID and results are directly transmitted to the LIS. The Barcode reader reads reagent ID (Lot and Expiry) and consumable ID for verification and release.

'The remarkable details in every single component are achieved by selecting only premium suppliers,' Teco adds. 'The performance of a high level instrument strongly depends on the concept in general and the perfect usability to reach the requirements of a modern laboratory analyser. Priority number one was to achieve daily routine reliability and easy-to-use operation.'

Dramatic advances in machine learning and image analysis

Deep Blue meets Hematoxilin and Eosin

In the nineties Deep Blue, the famous chess computer, defeated Kasparow. Only a year ago Google's Deepmind managed to master the ancient Chinese Go, known for its utmost complexity. Today, machine learning is a topic in the mainstream media and we are awaiting computers to master the complexity of reading tissue sections. 'Is there a new Deep Violet out there?' asks computer scientist Dr Christian Münzenmayer

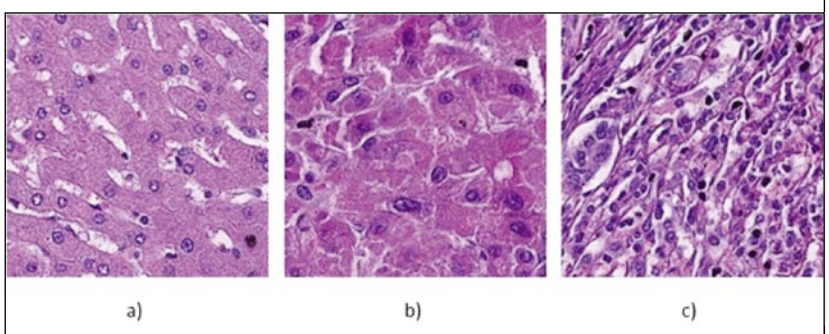


Figure 1 a) H&E stained liver tissue of healthy patient, b) Grade 1 (well differentiated), c) Grade 2 (poorly differentiated)

Christian Münzenmayer PhD MSc received his computational engineering degree at the German Friedrich-Alexander University Erlangen-Nuremberg and Computer Science doctorate from the University of Koblenz-Landau. At the Fraunhofer Institute for Integrated Circuits IIS in Erlangen since 2000, he became head of Medical Image Processing there in 2008. For his proposal on the automated analysis of micrographs of bone marrow smears he received the medical technology innovation prize in 2010, and the 2011 Boston-Scientific innovation award for his work on image-based classification of polyps in endoscopic images.

CT, MRI or PET scanners have placed radiology at the forefront of digital imaging in medicine. Fully integrated workflows within clinical information systems are tightly connected to large picture archiving and computer-assisted diagnostic algorithms, to detect automatically lung or breast cancer, provide second opinions, support digital workflows, thus paving the way for other disciplines. Hence, current clinical pathology can be compared to radiology 20 years ago, when X-ray images were reviewed on light boxes, film was physically carried and stored in large archives. Similarly, clinical histopathology still works with tissue samples prepared on glass slides, reviewed visually under microscopes and stored and transported in boxes. There is, of course, the complexity of three-dimensionality, of sectioning and staining, of variability in tissue, reagents and processes. Nevertheless, digitisation of pathology has begun.

Modern microscopy-based slide scanners are a key technology for digital pathology, which are e.g. offered by companies such as 3DHistech and Sysmex, Hamamatsu, Leica Biosystems, Olympus and others. Large-scale integrated solutions from companies such as Omnyx (GE/UPMC), Ventana Medical Systems (Roche) and Philips offer a capacity to scan hundreds of thousands of slides annually. Technical requirements on handling, transportation and archiving of such huge data is still among the major cost drivers slowing digital pathology adoption. Increasing demand of about 8-10% more slides per year and the increasing shortage of pathologists drive the need for automation and efficiency.

Biomarker research

Precision medicine, personal diagnostics and development of companion diagnostics basically drive biomarker research. Tissue micro arrays (TMA) are among the most important methods for parallel processing of hundreds of samples to detect and verify specificity of biomarkers for cancer subtypes. Automated support to generate high-quality TMA with devices such as the 3DHistech TMA Grandmaster and services, like the 'next-generation TMA' (ngTMA) offered by the Translational Research Unit at the Bern Institute of Pathology, will further drive the demand for automated processing of digitised samples.

Parameters extracted from the digital whole-slide images (WSI) provide information about phenotypes, in addition to what next generation sequencing (NGS) can offer. Thus, quantification of morphology and biomarker expression produces real big data – a specialty of the industry leaders Definiens.

Estimation of infiltration depth, detection of mitotic activity and spreading tumour cells are important for colon cancer diagnosis. Being a new biomarker for metastatic activity, the identification and quantification of tumour buds is gaining importance and is an active clinical research entering routine diagnostics. Such buds are defined as single tumour cells or clusters up to five cells in the tumour stroma separating from the main tumour and may be detected in H&E or pan-cytokeratin staining.

Having high potential to stratify patients for neoadjuvant therapies, and to forecast lymph node metastasis, consensus guidelines are under development. Automated detection and quantification methods we are working on may support this process in the future.

Another important factor in prognosis and treatment aiming for precision medicine is the determination of cancer stem cells (CSC), known for their resistance to chemotherapy and involvement in tumour recurrence. Using immunohistochemistry with CSC markers like CD13, CD133 and others is one way to identify CSC (cmp).

In our work we aim to identify CSC presence on ubiquitous H&E staining as an inexpensive tool for routine histopathology based on their distinct morphological features. Applying 'texture analysis' and deep learning methods we reached grading accuracies in the >90%. Finally, image analysis may provide workflow improvements that will unleash gains in efficiency needed to keep pace with the ever-increasing workload in laboratories and is promoted by industry leaders such as Philips. In view of the still low number of marker quantification products cleared for clinical use and an estimated 70% percent of routine cases that are handled in H&E without further markers, there seems to be a high potential to improve routine workflows.

An automated pre-analysis can check the quality of slides for tissue folds, staining problems, artefacts or scanning faults – factors that are also important for Biobanking where Charité is active. In a fully digital routine laboratory this can be used to re-order another slide and update the work list.

Automated detection of tumorous regions in the H&E also can be used to order other stains according to pre-defined panels and thus optimise time and resource usage to present the pathologist with a 'complete' case, including all necessary stainings for immediate diagnostic decisions. Advance measuring and counting markers can further reduce pathologist's idle time. Image registration can help to pre-align serial sections for intuitive navigation and provide virtual double-stainings, as provided by companies like Visiopharm or MicroDimensions.

Technology

The classical approach to pattern recognition and image analysis works as a serial pipeline of processing steps. Today, these steps may no longer be separated so strictly and may also have feedback loops included.

This pipeline starts with the sample being digitised in the scanner and results in a digital (whole slide) image for further processing. Image pre-processing as the next step typically includes geometric and colour normalisation, or deconvolution, to remedy variations in sample preparation, staining and scanning. Image alignment via so-called registration algorithms may be considered as a (fairly complex) pre-processing step.

The next step is segmentation of the WSI into separate objects, which may be slide sub-regions, cell clusters, cells or nuclei. For the automated analysis of WSI the main focus is often on the segmentation of cell nuclei and there exists little work that explicitly uses features of cytoplasm and stroma, although some researchers have hinted at the need for such features. Similar to the pathologist working from low to high magnification when analysing a slide a multi-resolution approach has been used to classify and retrieve high-resolution whole-slide histopathology images. To characterise individual objects, e.g. cells and cell nuclei classically features, mimicking cytologic features have been used.

The architecture of the tissue can be characterised by quantifying spatial distribution of nuclei implemented by mathematical graphs. Thus, the mathematical framework of graph theory can be used to extract quantitative features that are correlated with tissue structures. A complementary approach quantifies complex patterns in WSI by so-called texture analysis. Frequency analysis using wavelets and Fourier Transforms, statistical co-occurrence histograms, non-linear statistical geometrical features or local binary patterns to name just a few representatives, are powerful approaches that we combine with automated parameter optimisation and feature selection in the development of such systems. The final step in pattern recognition are the classifiers that decide, based on the object features if, for example, an image region may be considered benign or tumorous. Classical approaches are the 'k-nearest-neighbour', support vector machines, decision trees and neural networks. As mentioned, in recent years the so-called deep learning and convolutional neural networks (CNN) gained increasing interest and application also in digital pathology.

CNN are an extension of the self-learning artificial neural networks (ANNs), which had been an important research topic in image analysis and artificial intelligence in the mid-1990s. With the computing power of multi-core CPU, graphical processing units (GPU) and high-performance computing (HPC) combined with appropriate learning algorithms now available, such networks can be trained with far more layers in a decent amount of time. In contrast to ANNs, CNNs make use of up to twelve or more layers of data processing. Secondly, within the original ANNs, feed-forward, back-propagation architectures needed adequate and representative input data to converge to a stable and robust classification scheme. CNNs specifically incorporate this feature-extraction and selection process directly in the convolutional lower layers of the CNN and thus promise to reduce the need for application-specific and expensive application development as we could also retrace in several of our projects on histopathology, blood cell counting in bone marrow and malaria detection.

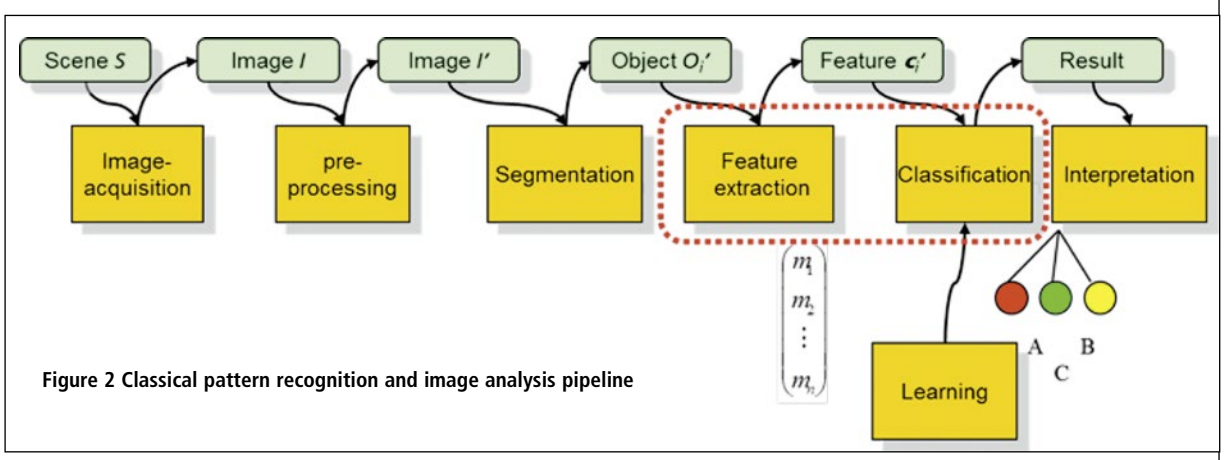


Figure 2 Classical pattern recognition and image analysis pipeline

Applications

Typical applications for image analysis in digital pathology are marker quantification, biomarker research and workflow improvements.

The classic example for marker quantification is proliferation counting for breast cancer diagnosis. Tissue sections immunohistochemically stained with an antigen to Ki67 display proliferating cells in brown tones against the normal cell nuclei in blue. The tumour region may be selected within the slide or using serial sections the tumorous region may be detected in the hematoxylin and eosin stain (H&E stain) and co-registered to the Ki67. An automated counting software, e.g. as developed at Charité, will obviously come up with more accurate and quantitative results compared to a pathologist's estimate, provided standardisation, sample and staining quality is ensured.

Conclusion

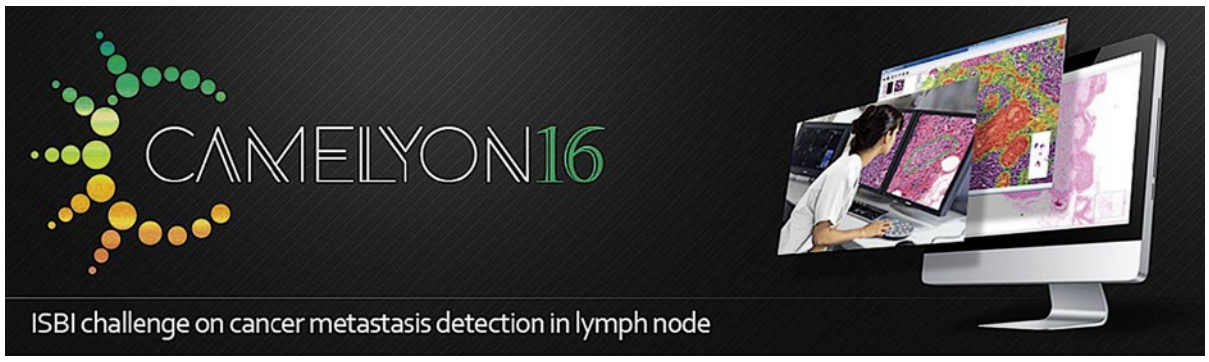
Undeniably, dramatic developments have occurred in recent years in machine learning and image analysis, reflected in research papers as well as high dynamics in industry – considering activities of Google, IBM Watson, Facebook, nvidia and others. This trend from the mainstream already has had a high scientific impact on digital pathology and will create new business opportunities for technology providers. Considering digital pathology, experts, industry and market studies agree that automation is one of the key drivers to adopt this technology and image analysis will play a major role in it.

The tipping point for digital pathology

Computational pathology

Digital pathology has been the next big thing for about a decade. Yet, today only a few pathology laboratories are fully equipped to digitise their workflow, mainly for legal or financial reasons. In the USA, for example, the 'struggle' with the FDA has prevented large-scale introduction of whole slide images (WSI) in pathology for years. Nevertheless, it remains to be seen whether many pathology labs would invest the required (large) amount of money in a technique that still has to substantiate those high expectations.

Will WSI be the disruptive innovation, as some experts believe? I think it will, but only under the right conditions. Yes, it may streamline the laboratories' diagnostic workflow, but only if fully and properly integrated with current workflows and information systems within the pathology department. WSI may be disruptive in the way we practice pathology at large, but only if we can create the right infrastructure to support networks of collaborating pathologists. Then it will be possible to practice 'pathology in the cloud' and instantly reach the right (subspecialised) pathologist for every difficult case. Disruptive as this organisation may be, perhaps the most important promise of digital pathology is the development of computational pathology algorithms for WSI. Once a computer can help a pathologist to interpret histopathological images, digital pathology will realise its full potential. Almost all research so far has been devoted to quantifying immunohistochemistry. The next step will be assessment of regular H&E stained sections. There are three (overlapping) areas in which computational pathology will have a major affect pathology diagnostics, with increasing level of impact and complexity.



- Computational pathology will increase efficiency of routine tasks. The first use cases for computational pathology will probably address tedious routine diagnostic tasks needing great accuracy, e.g. finding metastases in lymph node sections, or counting mitotic figures in breast cancer sections. Most pathologists are not fond of such tasks though they must be done well – they have high relevance for patient treatment planning. A computational pathology algorithm that can automatically detect metastases or count mitoses will alleviate these tasks and increase accuracy.

- Computational pathology can improve accuracy of tasks in which some grading is involved. Pathologists possess, at best, moderate reproducibility in such (semi-)quantitative tasks. A well-known example is Gleason scoring for prostate cancer. Computational pathology may offer a powerful alternative, by quantifying tissue changes that correspond with tumour grade in an accurate and reproducible manner.

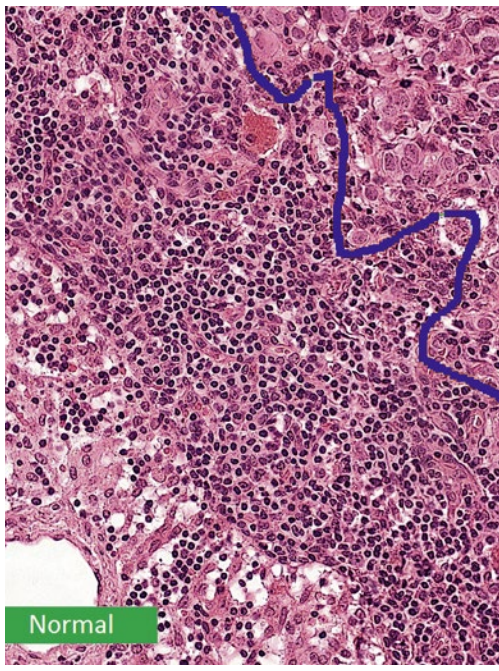
- Computational pathology may yield relevant information for diagnosis and prognosis that the human eye and mind are unable to recognise or appreciate. Instead of using a computer to mimic a pathologist in, for instance, grading a tumour, we could also try to obtain relevant quantitative data directly from WSI. These 'imaging biomarkers' may drastically change the way we extract information from tissue sections. While promising, a significant amount of research and validation is needed before a patient benefits from this type of application.

Researchers will have to develop and validate algorithms before computational pathology will really take off. Deep learning, a modern pattern recognition technique, is extremely powerful in many different disciplines and for a wide variety of problems. We have recently shown (Litjens et al. Scientific Reports 2016) that deep learning is also particularly suited for analysing WSI. We found that deep learning yielded computational pathology systems that are close to being clinically useful.

The 'Camelyon' grand challenges

To get a broader view and establish the current state-of-the-art of computational pathology for a specific application, we organised the 'Camelyon' grand challenges (http://camelyon16.grand-challenge.org and http://camelyon17.grand-challenge.org) – a valuable instrument in medical image analysis, in which every researcher or research group is invited to develop an algorithm for a given problem. All participants solve the same problem, using the same set of data, and the challenge organisers evaluate all submissions in exactly the same manner. Therefore this is a great way to compare different approaches to problem solving.

In the Camelyon16 challenge, we offered participants a large number of full WSI of sentinel lymph node sections of breast cancer patients



Dutch platform going live within 12 months

Augmenting pathology image exchange

Report: Mark Nicholls

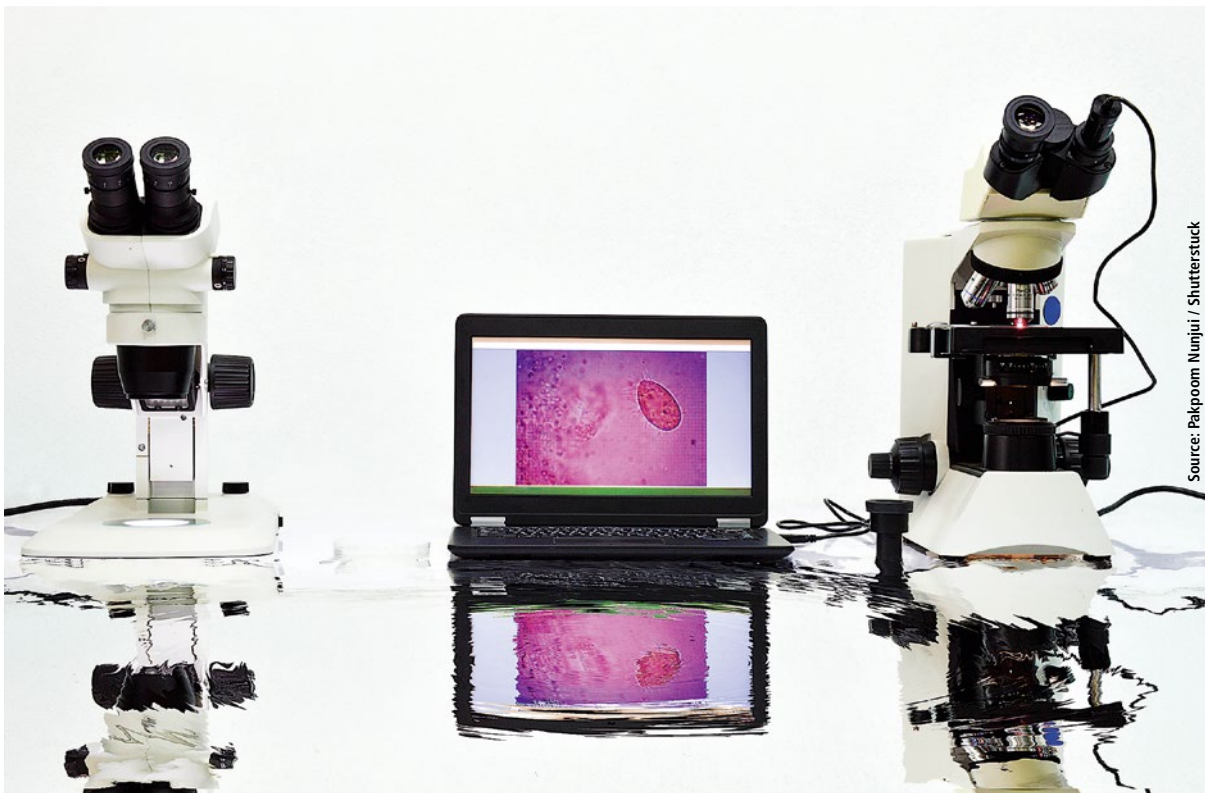
A national pathology image exchange platform for The Netherlands is expected to be in place and operational within the next 12 months.

The Pathology Image Exchange (PIE), which unites 45 pathology laboratories across The Netherlands, will facilitate quicker revision and re-evaluation of images and second opinions leading to more rapid diagnosis and better care for patients.

This December, Paul van Diest, Professor of Pathology at the University Medical Centre in Utrecht, will update the Digital Pathology Congress in London on the progress of PIE, the Dutch National Platform for IT in Pathology.

Pathologists' meetings are no longer physical

Speaking ahead of the event, he told European Hospital that he expected the tender process to be complete by December and in working with a chosen partner, hoped the platform would be operational by as early as summer 2017. All pathology laboratories in the country will be able to connect to the platform and exchange images, especially whole slide ones. 'It means if there are cases where we want to do an external consultation, we can do that through that platform and if there are revision cases where patients move from one hospital to the next and the pathology material needs to be re-evaluated or revised, we can do that much quicker than we now do by regular mail of the tissue sections,' van Diest said.


Source: Pakpoom Nunjui / Shutterstuck

Another benefit: rather than pathologists physically meeting to review interesting cases and come up with a consensus diagnosis, they will be able to do that through the platform.

The time is right to move to digital

Why had the Dutch pathology network embarked on this initiative now? 'I think the best answer to that is simply that the time is right,' Diest replied. 'Many Dutch labs are now turning digital and we realise there are a lot of things we can do quicker and with much higher quality and lower threshold consultation through such a platform.

So, when we started talking about this, we quite quickly agreed on the fact that it was a good idea.

Big advantage: A national pathology database

'I think a number of different countries around the world would like to have such a platform because the advantages are so obvious and hopefully we can serve as an example of what can be done and be copied by other countries.'

However, Professor van Diest does point out that the Netherlands has a significant advantage in this respect with a Dutch national pathology database – The PALGA Foundation (the nationwide network and registry of histo- and cytopathology in the Netherlands) – already in place, having been set up in 1971.

All Dutch pathology labs are connected to the database and over-

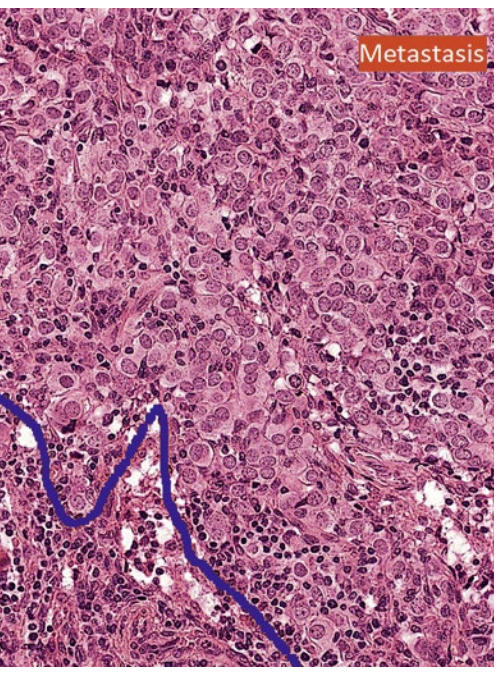
with exhaustive annotation of all metastases. We collected tissue sections in two different Dutch hospitals and scanned these on two different WSI scanners. Participants used these WSI to develop computational pathology algorithms. In the next stage of the challenge, participants ran their algorithms on a separate set of 130 sentinel lymph node WSI (this time without the 'ground truth' annotations) and we received their results for evaluation.

An important result is that many strong research groups worked on a very specific, clinically relevant application in histopathology, with a large set of fully annotated WSI, in a direct comparison. This definitely sped up developments, challenging researchers to spend significant time on a problem they would otherwise not tackle. A number of strong algorithms for this task resulted. Deep learning was applied in the top 10 algorithms, underlining the superiority of this technique for computational pathology. To our surprise, the best algorithms in Camelyon16 performed almost at the level of a pathologist participating in the challenge! We had expected computational pathology to be a powerful and promising development but hadn't expected this level of performance at this stage. However, before we can start implementing computational pathology we have to validate these algorithms rigorously on a large number of cases.

My strong conviction is that implementing computational pathology will tip the business case completely and even improve pathology diagnostics. But a significant amount of work is needed. Development and validation of computational pathology algorithms mostly require the involvement of expert pathologists. However, the rewards are huge: a modern, accurate and reproducible assessment of human tissues facilitating the best treatment of every individual patient.

An associate professor and group leader at the pathology department in Radboud University Medical Centre (RUMC) in Nijmegen, The Netherlands, **Jeroen van der Laak PhD Msc** (computer science) leads a computational pathology research group. Internationally rated among the leaders in this field, the research team develops and validates deep learning algorithms to improve efficiency in pathology diagnostics. He has co-authored over 80 peer-reviewed publications, is a member of the Editorial Boards of Laboratory Investigation and of the Journal of Pathology Informatics and sessions organiser for the European Congress of Pathology and Pathology Visions. In 2016 and 2017 he coordinated the Camelyon grand challenges.

Example of a metastatic region



Paul van Diest is Professor of Pathology at the University Medical Centre in Utrecht, The Netherlands, where he has headed the department since 2003. Adjunct Professor of Oncology at the Sidney Kimmel Oncology Centre at John Hopkins in Baltimore, USA, he has served as president of several international societies and published more than 600 papers in peer-reviewed journals.

night send all pathology reports to this central database.

The foundation will also oversee the PIE platform and be pivotal in ensuring the exchange of images is conducted in a patient-safe manner, ensuring patient confidentiality is not breached.

Better diagnosis, quicker second opinion

'The patient will benefit from this because consultation among colleagues will be more low-threshold than it is today and the frequency of that is going to dramatically increase once we have the platform in place,' van Diest explained. 'That means we will make better diagnoses and patients will get a second opinion or consultation much quicker than they do now.'

The Leeds Digital Pathology Project

Europe's most advanced histopathology unit

Among the earliest centres to embrace the concept of digital pathology, the Leeds Digital Pathology Project began in 2003 thanks to a Department of Health grant. Today the centre is Europe's largest.

Led by consultant histopathologist Dr Darren Treanor and covering research and clinical applications, the centre has eight scanners to scan 3-5,000 slides a month. It also has the world's largest digital pathology website, with 100,000-page requests in April 2017 and 10,000 visits a month (www.virtualpathology.leeds.ac.uk), and a slide library with 6,500 whole slide images. 'We believe we have the largest single site digital pathology installation in Europe, in terms of scanning instruments and scan throughput,' Treanor estimates.

The Leeds research covers two main areas: (a) supporting preclinical and clinical research with digital pathology offering scanning services, as well as some 3-D reconstruction and image analysis services for researchers; and (b) research into digital pathology.

The centre runs about 30 clinical trials

'We aim to understand and push the boundaries of digital pathology,' Treanor adds. 'Our research divides into technical innovations, having developed multiple systems at Leeds, and clinical applications where the team is interested in the adoption of digital pathology including understanding the barriers to adoption, and the safe uptake of digital pathology.'

Work to perform the first systematic review of the accuracy of digital pathology led to follow on work from Dr Bethany Williams – the first digital pathology leadership fellow in the world.

With its early start, Leeds could lead the way in technical advances and develop systems for several applications including: tissue microarray analysis; in-house image analysis; 3-D registration and reconstruction software; and systems for manual assessment of tumour stroma ratio (a web-based tool for systematic random sampling of virtual slides). The centre also developed colour measurement and a colour calibration slide for digital pathology in collaboration with a vendor, FFEI Ltd.

'This is the only tissue-mimicking colour calibration slide available, a prerequisite for accurate colour calibration of digital pathology,' Treanor points out. However, the major development has been the Leeds Virtual Microscope (LVM). 'We identified a big problem with digital pathology – that the software used to view images was 60% slower than the microscope.'

Working with collaborators in the university's School of Computing (Professor Roy Ruddle), they set out to create a viewer as fast as a microscope. The successful output was software, licenced to Roche.

The LVM runs on systems that range from laptops, to high-definition medical displays, and 50 megapixel 'Powerwalls', used to train pathologists. It has been deployed across the Yorkshire and the Humber region's 16 pathology laboratories for pathology training.

The LVM also won the Medipex innovation award for medical imaging in 2014.

The Leeds unit is nearing complete digitisation. In the university laboratory, virtually all research slides are scanned, and is now developing within the NHS department. 'In 2016, we started a pilot deployment in breast pathology and have seen very reassuring results of this, with four pathologists using digital pathology for their diagnostic work,' says Treanor.

This year saw a partnership with Leica to deploy digital pathology for primary diagnosis across all clinical specialties. This involves 45 consultants, 30 trainees, 250,000 slides per year and 100TB of data. It also includes workshops about digital pathology, including laboratory implementation and clinical validation.

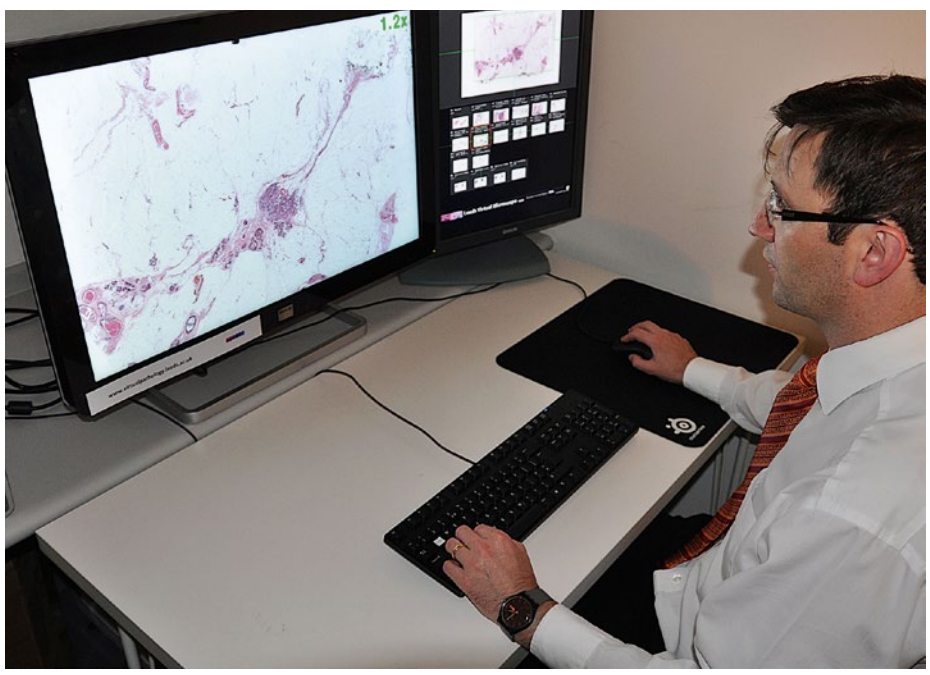
However, Treanor acknowledges there have been challenges over the years to digital pathology adoption, particularly in four critical areas: virtual slides were slower than the microscope; confidence in accuracy was not assured; the cost-benefit was not established; and pathologists were reluctant to adopt.

For Leeds, LVM addressed the speed issue, and a systematic review showed that, while there have been many validation studies, the overall quality of the evidence has not been uniformly high.

'From this, we developed our own validation protocol that allows pathologists to learn by comparing the microscope and virtual slide over a period of several weeks during normal clinical practice. So far,' he adds, 'this has allowed us to be much more confident when diagnosing digitally.'

The team now plans to address the issues of cost benefit and wider adoption of the technology. 'Pathologists need evidence that it works,' Treanor remarks. 'If we can provide them with an effective user interface, good workflows, and assure them of diagnostic quality, while establishing the cost-benefit, we see no reason why Digital Pathology would not be adopted for clinical practice.'

The Leeds team collaborates with a number of companies – Leica customers from the beginning; developing a colour calibration system for digital pathology imaging with FFEI Ltd; and selling the LVM system to Roche.



Dr Darren Treanor is Consultant Histopathologist at Leeds Teaching Hospitals NHS Trust and Honorary Clinical Associate Professor at the University of Leeds,UK. He is also Guest Professor in Digital Pathology at Linköping University, Sweden, where he works with the university and hospital teams on digital pathology research in a well-established project where 100% of clinical slides are scanned.

Considerable benefits and opportunities

'On the research side, it would be unthinkable to run a clinical research lab without digital pathology,' Treanor believes. The 'enormous advantages include workflow; archiving and image analysis 'On the clinical side, our breast pathologists report great satisfaction with their digital pathology adoption so far. They love the improved workflow, and the ability to work without glass slides. Ordering and reviewing additional stains, for example in immunochemistry, is much easier.'

From the university aspect, the team manages its own data storage, presently with about 160TB, with a large number of application servers hosting the different systems. Within the NHS element, they expect to produce 100TB of data annually, when the full deployment is up and running.

However, he suggests the amount of data should not be daunting – when they began doing digital pathology in 2003, a 4TB system cost over £100,000. That amount of data can now be stored on a single disk drive.

'A modern hospital should be able to handle large data sets and I'm confident that data storage requirements will become less of an issue as storage systems improve in future. Hospitals also need to understand that, while the data volume may be large, only a small percentage of that needs to be on fast storage systems and digital pathology is very amenable to inexpensive archiving solutions.'

Sharing slides with other pathologists is a major part of the Leeds team's ethos and service. From its website, all educational and research slides are freely available for pathologists, scientists, medical students and the general public.

On the clinical side, the system allows easy access over a secure VPN connection for Leeds pathologists to view the images remotely.

Sharing work is a key benefit of digital pathology, he says, pointing to two benefits. We can give second opinions for colleagues in regional district general hospitals; but with digital pathology we can give feedback immediately, with live interaction. Secondly, as a large teaching hospital, we see opportunities to use digital pathology to share work around the region, ironing out peaks and troughs in our capacity and demand.'