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The potential role of ACE2

As COVID-19 continues to jet and alight invisibly around the globe, scientists now report that the virus has mutated to become two strains: the older 'S-type' appears milder and less infectious, while the later-emerging 'L-type', is more aggressive, spreads more quickly, and currently accounts for about 70 percent of cases. Worldwide, medical researchers are exploring whether existing viral treatments just might work against the new strains as well as examining which current research should speed into trials. In Australia, researchers have reasoned that a well-known HIV drug could work against the new coronavirus, for example, whilst other reports indicate that Chinese scientists have seen success in delivering high intravenous doses of Vitamin C to seriously infected patients (The journal Caduceus also reports that large shipments of Vitamin C are now enroute to that country). Meanwhile, ACE2 raises hopes as a rational therapy against this devastating viral attack.

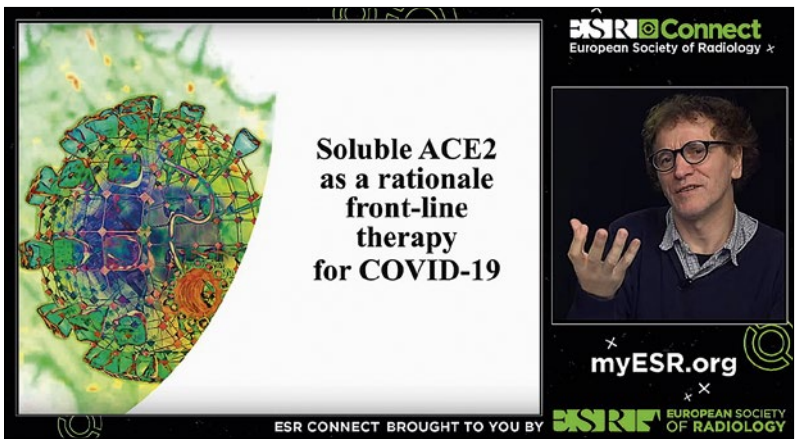
Report: Mark Nicholls

Scientific hopes are that the angiotensin converting enzyme 2 (ACE2) will play a critical role in tackling the COVID-19 pandemic. During a live webcast lecture *'ACE2 – a rational frontline therapy for COVID-19'*, organised by the European Society of Radiology, the enzyme's background, development and potential role as a therapy was explored by one of the world's leading geneticists and molecular immunologists.

Professor Josef Penninger outlined the relationship between ACE2 and the renin-angiotensin system (RAS) – responsible for systemic vascular resistance and for regulating blood pressure and fluid-electrolyte balance in instances of lung injury – highlighting the predisposition of ACE2 as a SARS-CoV and SARS-CoV-2 receptor and potential treatment approach.

Starting more than two decades ago, the research led to the discovery of ACE2, initially in fly and mouse models and then indicating a human link and, the expert explained, how more recently that has led his team to believe they are closer to testing a medicine for COVID-19.

From a knockout mouse model, they found that, if ACE2 was lacking then heart function was impaired, and was a negative regulator of the RAS. This also pointed to a possible gender bias in COVID-19 – with ACE2 on the X chromosome, meaning males have one copy and females two.



Professor Josef Penninger during the ESR live webcast on COVID-19

'In simple terms,' Penninger said, 'ACE cleaves to amino acid from angiotensin 1 to make angiotensin 2, which acts on receptors 81 and 82. ACE2 is a catalytically active molecule on the surface of cells – though it can also be soluble in serum – and inactivates this pathway.'

From there, the research showed that ACE2 also affects kidney disease and regulates liver and lung fibrosis. 'If you knock out ACE2,' he continued, 'disease gets much worse and if you have ACE2 it gets much milder because it counterbalances the ACE function and, by doing so, regulates the system.'

With a lack of ACE2 in the lung leading to severe injury, research by other groups in the early 2000s had indicated that ACE2 might be a receptor for the SARS coronavirus of 2003. With the explanation of SARS binding to ACE2 and enhancing disease severity, his team saw a new pathway to develop a medicine against acute lung injury. 'Based on this,' Pennington explained, 'we decided to develop a human recombinant angiotensin renin converting enzyme for the therapy of lung injury.' He also highlighted the difference between the SARS virus of 2003, which infected about 8000 people leading to 800 deaths, and COVID-19. For SARS to spread, a patient had to be very ill and in close contact with other individuals to transmit, whereas the new virus is easy to transmit. 'That's why there is fundamental difference between old outbreak and new outbreak.

'What we believe is happening is that the virus comes in via this spike protein, binds to ACE2 and together with ACE2 gets into the cell, fuses to the membrane, the virus gets out from the endosome, and replicates. So, ACE2 is essential for binding to the virus and surface – of course this leads to viral release and replicates and then spread, leading to diseases we know as SARS and COVID-19,' Penninger explained.

Currently, Apeiron Biologics AG, a company founded by Penninger, is scheduled to start a pilot clinical trial for a newly-developed drug designed to decrease mortality in those affected by the virus.

'This is where we believe our soluble ACE2 would come in,' he explained, 'Because ACE2 sits on the membrane and our molecule is soluble, it would soak up the virus like a neutralising antibody, so the virus cannot find its real receptor. With less virus coming, this would slow down viral infection and improve disease because the virus cannot properly get in and infect the cells.

As one of the world's leading geneticists and molecular immunologists, **Professor Josef Penninger** has gained numerous awards for his work and research and he is also author of around 1100 publications. He established the Viennese Institute of Molecular Biotechnology and is the current Director of the Life Sciences Institute at the University of British Columbia in Canada. The main focus of his work has been autoimmune, bone, and heart and lung diseases, and cancers.

'We believe, based on the discovery of ACE2 – and its function as a negative regulator of renin angiotensin, protecting heart, kidneys, liver, protecting the lung – this would make sense as a therapeutic for COVID-19.'

This, he concluded, would have two functions – taking the virus away from its real receptor by working as a neutralising antibody and, second, protecting tissues – as in the lung – from the disease.

Penninger emphasised that carefully designed placebo controlled trials in COVID patients are now needed to test the science.

Hospital heroes

STAY HOME – SAVE LIVES

Around the globe, care staff and physicians are working beyond their limits to help COVID-19 patients. They are our modern heroes, risking their own health to save lives – faced with a highly contagious virus, sometimes without adequate protective equipment. Physicians and nurses at Raphaelsklinik in Münster, Germany, have a message for all of us: "We stay here for you, please stay home for us." Only if we stay at home we will neither acquire the virus nor pass it on to other people. This is the only way to keep COVID-19 from spreading.

Photo: Raphaelsklinik Münster/Michael Bührke

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Inspiration against COVID-19

Taiwan: a role model for pandemic management

As many nations struggle to keep COVID-19 infection numbers down through increasingly tough public health measures, some point out the island of Taiwan presents an example of how to be prepared in the event of a pandemic.

Located less than 150 kilometres from the original viral source – China – Taiwan has seen far fewer cases of the coronavirus in the past month, with a much lower infection rate. What may be at first surprising is the result of quick and decisive action taken by the central government as soon as the news of a virus emerged from the Chinese city of Wuhan. It is also worth noting the practices utilised by Taiwan's hospitals as they seek to curb the virus and protect patients and medics.

Smaller staff groups reduce infection risk

One key step taken early was the reduction of the work group sizes within medical facilities. This reduces the risk of a community spread within the hospital emerging from infected patients being treated. Depending on the size of the staff handling an area of the hospital, and the number of patients being overseen there, one infection could jeopardise the safety of an entire ward.

As a result, Taiwan's major medical facilities worked to limit the size of work units, reducing them by as much as two-thirds. In other words, fewer staff members are responsible for fewer patients, although the ratio remains constant. This allows for greater control over the spread of infection while keeping treatment standards intact. Steps were also taken to control the flow of patients and visitors into hospitals quickly. Shih Chung-Liang, a top official for Taiwan's Central Epidemic Command Centre (CECC), announced that hospitals were establishing separate entrances and exits for in- and outpatients, plus A&E patients, to help prevent the spread of infection via regular hospital traffic. In effect, hospital entry began to resemble airport customs, with visitors passing through a temperature checkpoint and showing IDs before admittance. Combined with stricter regulations for cleaning and disinfecting hospital areas, Taiwan's hospitals have been able to effectively lockdown the virus treatment environment.

Before entering the Taipei Medical University Hospital, visitors must pass an infrared thermometer checkpoint and present their personal health card

Maintaining a high bed-per-capita ratio

At the beginning of April, as the global total of infections neared 700,000, with over 30,000 deaths, Taiwan's count stood at 300, with only five deaths. From those cases, approximately 75% were patients who had been abroad or directly in contact with someone from overseas in recent weeks.

Though totals have remained remarkably low, the Taiwanese government has prepared a backup plan to handle a sudden jump in cases, if it should emerge despite the aforementioned precautions. Many countries have found that they do not have nearly enough hospital beds to care for patients suffering from a highly infectious disease like COVID-19.

In response to this concern, the Deputy Director for the Taiwanese Centre for Disease Control (CDC) Chuang Jen-Hsiang stated that the country has nearly 1,000 negative pressure isolation rooms available, with the capacity to add significantly more through room reconfigurations. This is a remarkably high number, given the relatively small population of the island, and speaks to the country's preparedness and advanced medical infrastructure. As the number of infections continues to rise, these isolation rooms will be critical to prevent community spread within healthcare centres.

Teamwork pays off

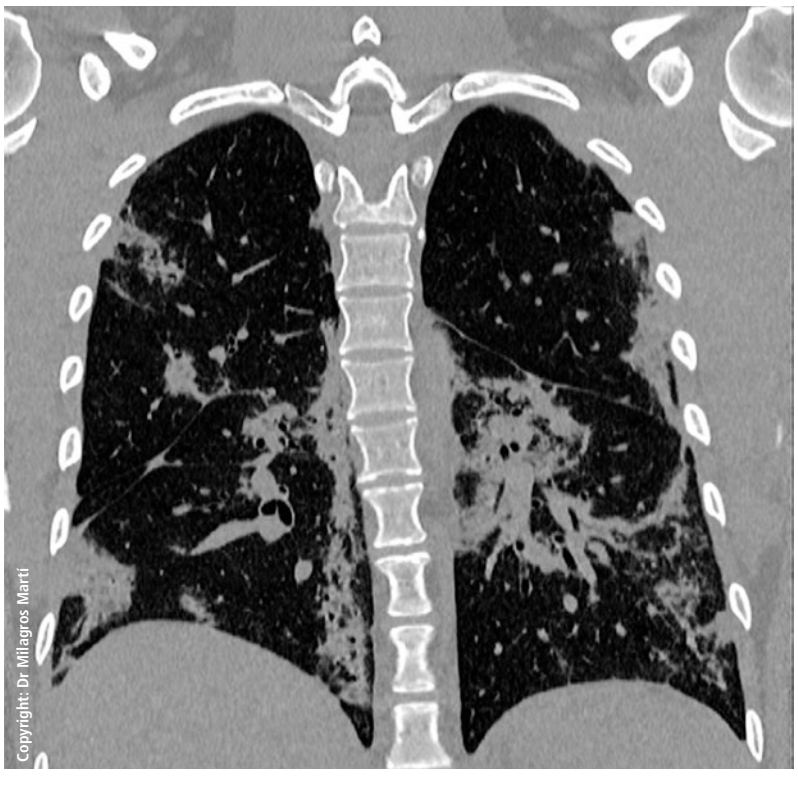
Finally, Taiwan has benefited greatly from the close coordination between its hospitals and central government. Within the country's nationalised healthcare system, every citizen and resident is assigned a health card, embedded with a computer chip reflecting their identity and medical history. This has enabled hospitals to quickly and efficiently control visitor entrance and report on patient symptoms, as well as share information across the island's major medical centres in Taipei, Kaohsiung, Taichung and other cities. Specifically, eight of Taiwan's largest hospitals have been very diligently sharing test data and results, allowing a broad collaborative effort to find the best ways to fight the virus itself.

Many of these counter measures can be easily duplicated by European countries. Thus far, Taiwan's biggest success can be attributed to how ready the country and its hospitals were from Day One, while other states were still assessing whether the virus was a threat to them at all. However, the willingness and effectiveness with which doctors and medical officials have worked to cooperate with each other and the public is a testament to the country's smart and rational approach to healthcare and disease prevention.

Today's recommendations might not be va

Imaging COVID-19

Chest X-ray is the first imaging method to diagnose COVID-19 coronavirus infection in Spain but, in the light of new evidence, but this may change soon, according to Milagros Martí de Gracia, Vice President of the Spanish Society of Radiology (SERAM) and head of the emergency radiology unit at La Paz Hospital in Madrid, one of the hot spots for viral re-production of COVID-19, Mélisande Rouger reports



EH: How are you coping with the outbreak at your hospital?

Milagros Martí de Gracia: 'We've been preparing for this situation for several days; the number of patients has grown progressively, and has surged this past couple of days. We now have 200 patients with confirmed COVID-19 coronavirus infection (as of March 12).

'Patients have been gradually placed in wards that can accommodate between 14 and 25 persons each. We have five wards dedicated exclusively to patients with suspected infection. 'Naturally, this has had an impact on the organisation of the emergency radiology unit. Patients with very high suspicion and confirmed infection are examined with portable radiology equipment. Suspicious patients are examined in the emergency radiology room, which is currently exclusively dedicated to this purpose. 'Patients without suspected infection are waiting to be attended or are located in other wards. Radiological examinations are done in another area of the hospital, away from the main area, so that patients do not mix.'

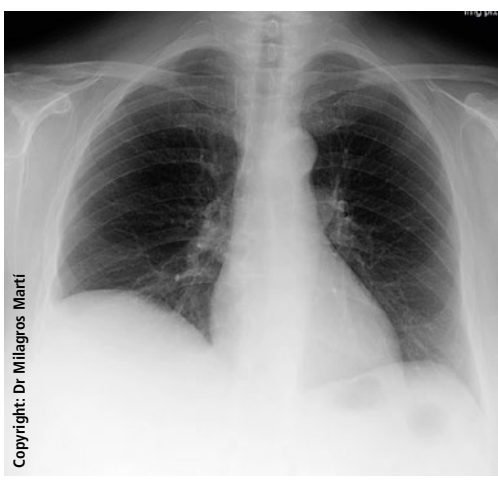
Coronal reconstruction via CT showing typical COVID-19 peripheral and subpleural alveolar opacities

How do these measures affect your department's workflow?

'The request for chest radiographs has grown exponentially and proportionally with the number of patients visiting the emergency department. A chest X-ray is performed in suspected or confirmed patients through specific circuits. Rooms with dedicated equipment are allocated exclusively for possible patients. Portable radiology equipment is available for confirmed or suspected patients. 'This is easier to organise when teams are dedicated exclusively to the emergency department, or when emergency radiology units are integrated in the emergency department.'

How many patients have you admitted so far?

'We attend more than 400 daily



No infection with COVID-19

emergencies only in the general hospital. Every day we receive around 140 alerts. Today, on March 12, more than 200 patients have been confirmed with the virus, many of whom have already been admitted.

'At first, the epidemiological criterion was the most important information, i.e. having travelled or contacted someone from China or Korea. Later the criterion was having had contact with someone infected or coming back from Italy. But now in Madrid, we only need to assess the symptoms, which are very non-specific (cough, fever and respiratory distress). However, there may be other symptoms that complicate suspicion. Analytical alterations such as

Nosocomial influenza

The effect of mask wearing is enormous

Interview: Katrin Schreiter

The Coronavirus dominates everyday conversation as well as medical and scientific discussions, but in a Leipzig hygiene congress, other topics – such as nosocomial influenza – took a strong position.

Dr Andreas Ambrosch, head of the Institute of Laboratory Medicine, Microbiology and Hospital Hygiene at the Brothers of Mercy Hospital in Regensburg, Germany, presented a new study on the spread of nosocomial influenza. But the question arises, whether this, in view of the new coronavirus, is this only an incidental topic. 'Not at all,' the hygiene expert exclaimed: 'Nobody knows whether the coronavirus will still be around next year. But we are confronted with influenza every year. At the moment, everyone seems to forget how many deaths are caused by viral influenza each year.'

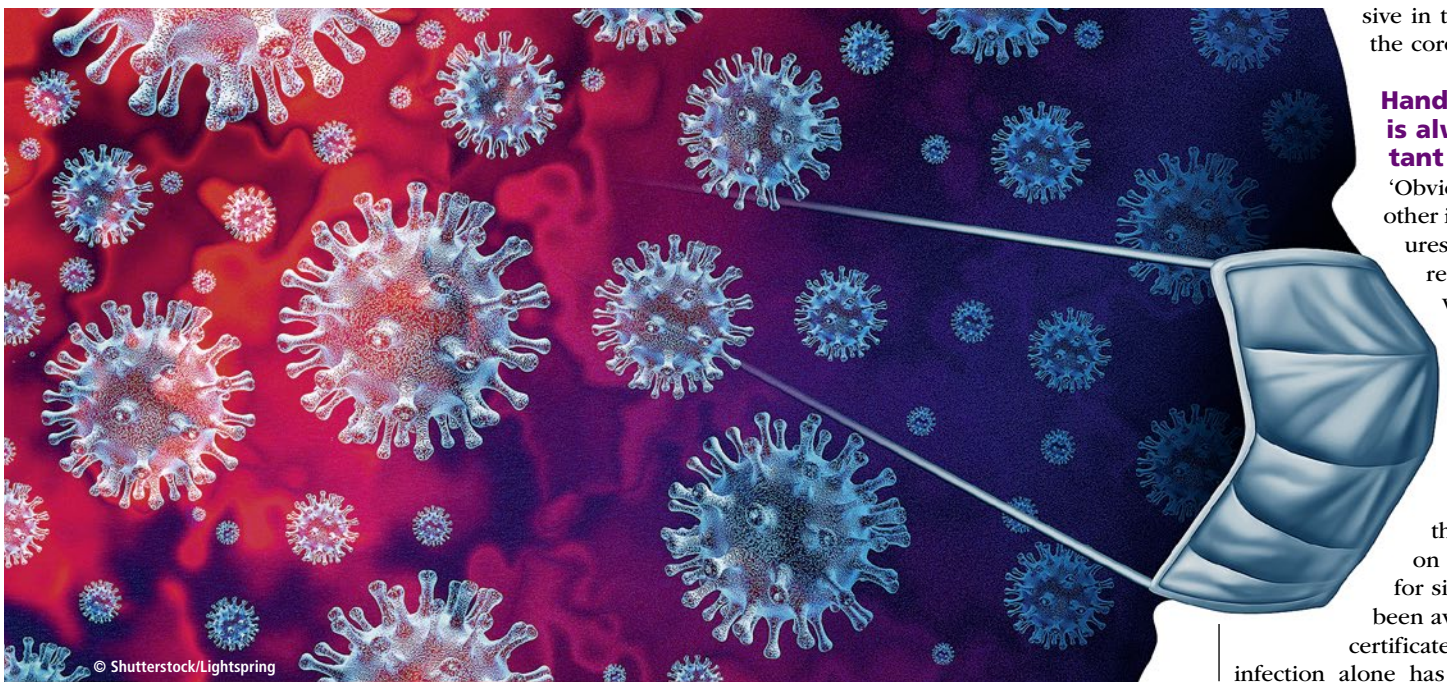
Reason enough for him to study the influenza virus intensively. He presented his current findings at the 6th Joint Congress of the German Society of Hygiene and Microbiology and the Association for General and Applied Microbiology, held in Leipzig.

Cancer patients are affected the most

'When influenza occurs in a hospital, it's particularly dangerous,' Ambrosch stressed. 'Up to 50% of influenza patients may die due to their underlying diseases.' Patients on oncology wards are particularly affected, as they usually have no immunity. By comparison, the mortality rate across the total population per season is less than 0.5%.

The expert uses these numbers to confirm that prevention can indeed save lives: Ambrosch has been working on a study about the spread of the influenza virus at the 1,000 bed Hospital of the Brothers of Mercy in Regensburg since 2015. As a result, since 2017, as soon as more than three influenza patients are on a ward, all staff members have had to wear mouth and nose protection during their entire shift. The objective was to lower the high nosocomial infection rate for influenza known at the hospital and other German hospitals by 20-30%. 'Eight hours – it sounds more dramatic than it is. But the protection is not really much of a hindrance during work,' the doctor confirms. 'The effect is enormous!' he adds, pointing out the numbers.

The hospital in Regensburg sees an average of 150-380 influenza patients annually. The relatively small change of wearing protective clothing has helped to lower the rate of new nosocomial infection by 60% (from more than 20% to just under 10%), Ambrosch reports. The number of mortalities has even decreased by 85%. In 2015 and 2016 respectively, there were seven nosocomial influenza victims in the hospital; afterwards there was a maximum of only one patient a year. Consistent mouth and nose protection are also decisive in the fight against the coronavirus.



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Hand disinfection is always important

'Obviously there are other important measures to contain, or respectively prevent, influenza,' Ambrosch adds. 'Hand disinfection is always important.' His hospital has been a member of the ASH – Action on Clean Hands – for six years and has been awarded the gold certificate. But, hand disinfection alone has proven not to be enough. 'Vaccination is the most effective measure,' Ambrosch is convinced. 'However, there are many shortcomings here, as the German OkaPII Study (online survey on influenza vaccination amongst hospital staff) has shown. The last nationwide survey was carried out in spring 2019, when 171 hospitals with around 27,000 staff participated. Result: only 76% of doctors have themselves vaccinated against influenza, and only 46% of nurses do. 'To ensure effective protection more than 85% of hospital staff need to be vaccinated.'

Willingness to be vaccinated at The Hospital of the Brothers of Mercy in Regensburg also leaves a lot to be desired: 'Only 57% of doctors are vaccinated, and only 34% of nurses. 'We are banking on education – but only make very small steps forward.'

Ambrosch's biggest wish regarding influenza: 'Vaccination should be mandatory for medical staff. This would be a really big step in the right direction.'

Dr Andreas Ambrosch is head of the Institute of Laboratory Medicine, Microbiology and Hospital Hygiene at The Hospital of the Brothers of Mercy in Regensburg, Germany. A microbiologist and Antibiotic Stewardship (ABS) expert, Dr Ambrosch has been working on an effective action plan for the protection of patients against so-called nosocomial infections – i.e. infections which patients acquire in the hospital – for the last four years.

lid tomorrow

Infection with COVID-19

lymphopenia, elevation of transaminases or lactate dehydrogenase augment the degree of suspicion.'

What is the protocol?

'Patients with respiratory symptoms must remain isolated and wear a mask. If clinical suspicion persists after the examination, a sample of nasopharyngeal exudate is taken to test reverse-transcription polymerase chain reaction (RT-PCR).

'Then, we perform a chest X-ray. Getting the results of the PCR test may take several hours. The chest X-ray is a discriminating element; if the clinical situation and the chest X-ray film are normal, patients can go home and wait for the results of the etiological test. But if the film shows pathological findings, patients are admitted to the hospital for observation.

'Usually the absence or presence of pathological findings on chest X-ray is determining to send the patient home or keep him/her under observation 'But if the clinical suspicion is high and the PCR or/and chest X-ray is normal, a chest CT is indicated. 'This is a fast-evolving issue and today's recommendations might not be valid tomorrow.

'The SERAM is developing and updating guidelines for radiologists that are available on our website. We have also created working groups to help not only diagnose the virus, but also to promote safe management among patients and healthcare staff.'

How important is radiology in diagnosing COVID-19 infection?

'Radiology is fundamental in this process. The radiologist's main contribution is to facilitate and expedite as much as possible the exploration, help design specific circuits and provide a fast and accurate report of the radiological findings that should indicate whether or not these are consistent with the COVID-19 coronavirus infection.'

What are the typical radiological findings?

'The findings that make us strongly suspect that we are dealing with a COVID-19 infection are the ground glass patterned areas, which, even in the initial stages, affect both lungs, in particular the lower lobes, and especially the posterior segments, with a fundamentally peripheral and subpleural distribution. These findings are present on chest CT in practically 50% of patients in the first two days; For this, in China, CT is being used as a screening or diagnostic method.

'These lesions progress in the following days until they become more diffuse. If they associate with septal thickening, they will present with a crazy paving pattern. In general, they progress in extension and also towards the consolidation that is done concomitantly with the ground glass pattern, which can present a rounded morphology. It is very rare that it associates lymphadenopathy or capitation or pneumothorax, as the Middle East respiratory syndrome coronavirus (MERS-CoV) did.'

Do you also use imaging to follow-up the disease?

'We have had little time to discuss our experience in the follow-up of infected patients so far. But, for the time being, radiology is playing a crucial role in the diagnosis and identification of patients for observation in the hospital admission or at home.

'The most commonly used diagnostic modality is chest radiography. At the moment, computed tomography (CT) plays a limited role and is carried out in cases of clinical mismatch and PCR, i.e. in patients with high suspicion of being infected but with negative or inconclusive PCR.

'CT is also indicated for the recognition of possible complications that are not obvious on the chest radiograph, or to diagnose very serious patients quickly, whose PCR results are not yet available, for placement in a specific coronavirus intensive surveillance unit.

'In other countries like China, CT is being used as a diagnostic modality because of its high sensitivity to show lung lesions before PCR. The WHO considers typical CT findings as a diagnostic criterion since February 17. 'We have published our recommendations on our website (https://www.seram.es), and will update them soon.'

After a decade of healthcare budget cuts in Spain, do you have enough equipment to face the outbreak?

'Certainly the high number of infected is a great challenge for public health in Madrid and Spain because we have suffered great cuts due to the crisis. In my department, a priori, we did not have enough equipment to face the crisis but agreements have been reached for its immediate acquisition of several digital portable equipment for the radiology department and mechanical ventilation equipment for the ICUs.'

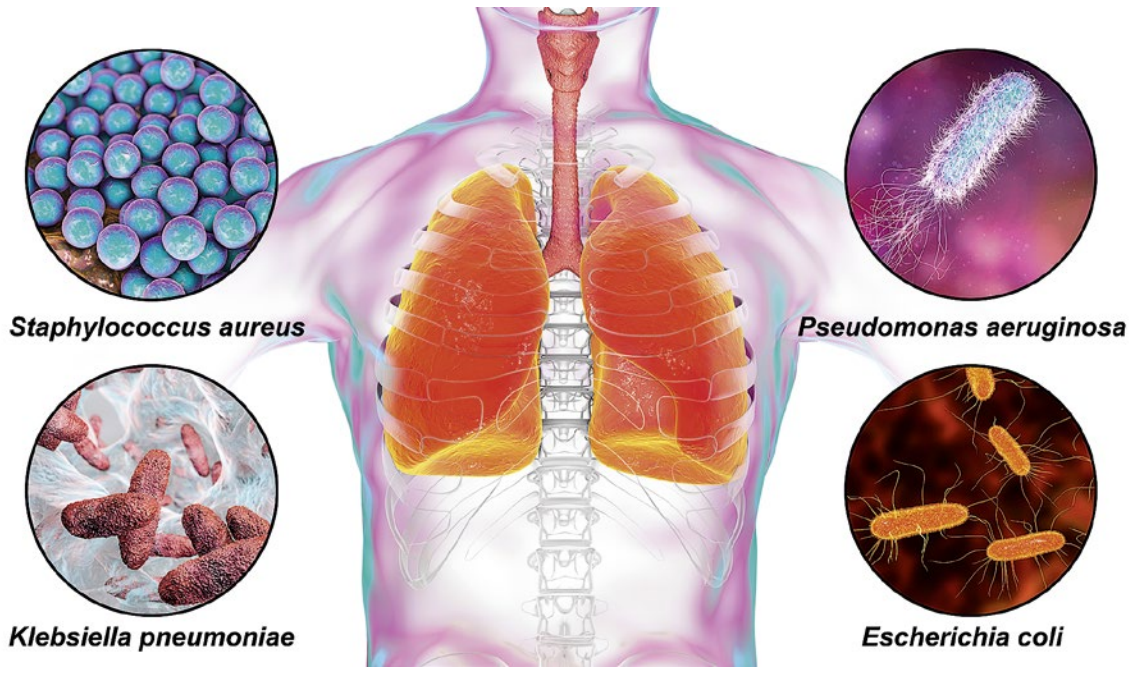
Milagros Martí de Gracia is Vice President of the Spanish Society of Radiology (SERAM), President of the Spanish Society of Emergency Radiology (SERAU) and head of the department of emergency radiology at La Paz Hospital, a general tertiary hospital in Madrid. She was President of La Paz's Catastrophe Committee from 2006 to 2019 and is now its Vice President. She is a founding member of the European Society of Emergency Radiology (ESER). A graduate from the Complutense University she gained her MD from the Autonomous University in Madrid, where she is Honorary Professor of Medicine.

'The hygiene plan is nothing but a fig leaf'

Where are the infectiologists?

Report: Anja Behringer

Nosocomial infections cause more deaths than traffic accidents – a stunning discovery made in a recent German study. Worse: infectious diseases long thought eradicated in Europe, such as measles, tuberculosis (TB) and, more recently, syphilis, are also implicated. The increasing number of patients places an additional financial burden on healthcare. But – and this might be the good news – hospital hygiene finally receives top priority in German hospitals. Hygiene campaigns began ten years ago and today sanitiser dispensers are ubiquitous throughout any hospital. Alas, to little avail. No significant improvement can be reported despite the fact that a slew of new professions and specialisations have been created: physician hygiene specialist, nurse hygiene specialist, hygiene risk assessor, or infectiologist. We appear to be losing the battle against hospital acquired infections (HAIs). The problem is exacerbated by an ageing population, more susceptible to diseases, and by antibiotics losing their efficacy.



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Hand hygiene – the be-all and end-all in the battle against microorganisms

What can be done? Hygiene was the dominant topic, dissected from back to front during the European Health Congress, held in Munich. Results were not particularly encouraging – passing the buck appeared to be the chosen approach. 'Wash your hands after going to the loo and before meals' – generations of children have learned this advice, and it's as valid today as 50 years ago; according to the World Health Organisation, 60% of all infectious diseases are transmitted by hand contact.

For Johanna Knüppel, expert and speaker of the German Nurses Association (Deutscher Berufsverband für Pflegeberufe – DBfK) in Berlin, the root cause of the long known and still unsolved problem is the glaring lack of staff, time and space. She does concede that the handwashing campaign did sharpen awareness, but, she asks, how do we disinfect? 'The quantifiable – and increased – use of sanitisers does not allow any conclusions as to the quality of the handwashing procedure. According to manufacturer information, the substance should be applied for 30 seconds. If nurses were to follow these instructions, they would spend 2.5 hours per day sanitising their hands.' No wonder, people try to cut sanitising corners – and increasingly, hospital managers understand the problem. Even the clinical bigwigs display 'organised neglect', as Professor Walter Popp, Vice President of the German Society of Hospital Hygiene (Deutsche Gesellschaft für Krankenhaushygiene) and Medical Director at Hykomed GmbH, in Dortmund, Germany, noted when he observed his colleagues in the operating room. It's not even hand sanitising that worries Popp but 'the way they handle patients with ears not covered'. A detail that goes unnoticed – and which is a symptom of the problem. The infection protection guidelines issued by the German Commission for Hospital Hygiene and Infection Prevention (Kommission für Krankenhaushygiene und Infektionsprävention – KRINKO) are increasingly vague, as Popp underlines. Moreover, he adds, nobody knows from where all the needed hygiene specialists are supposed to come; and, even if they did exist, they alone could not level off the heap of problems.

In 2015, a 10-point plan to push back HAIs and antibiotic resistance, published by the then German Federal Ministry of Health, was met with enthusiasm. One of the few clearly phrased items in the plan: a special program designed to recruit additional hygiene staff by the end of 2016. When, after a transition period, the hygiene recommendations became binding, the target date was moved – to the end of 2019. Recruitment turned out to be sluggish. The Federal Ministry of Health put the blame squarely on the hospitals and regional governments. What the ministry failed to see: candidates are not rejected by the hospitals; candidates simply do not exist. After all, working conditions in hospitals are not particularly attractive.

Hygiene is rising to a top priority

Whilst physicians are the worst of role models, nurses are busy trying to implement instructions that are not grounded in any reality – a reality in which patients who have not yet been screened for microbes are parked in a hallway until rooms become available and where cleaning service contracts are put out to tender each year and the cheap-

Raising data protection levels against cyber attacks

IT security: as routine as disinf

Report: Sonja Buske

Cyber attacks on hospitals occur every day. However, if IT security works well, nobody needs even notice. But if defence measures fail the impact can be enormous and the outcry among the general public large. The new branch-specific security standard (B3S) of the German Hospital Federation (DKG) shows how hospitals can improve their IT security. The Federal Office for Information Security (BSI) officially recognised this standard in October 2019; its implementation meets the legal requirements.

Hospitals are critical infrastructure operators and every two years need to prove to the BSI that they implement adequate measures of protection for their IT systems if they treat a minimum of 30,000 cases a year. 'The B3S is a very rigorous security standard,' explains Markus Holzbrecher-Morys, deputy managing director of the Department for IT, Data Exchange and eHealth at the DKG. He was majorly involved in its development. 'The subject of IT security is very important to us here at the DKG.

'The B3S lists 168 standards that must be implemented. However, realistically, not all points can be covered in one inspection and several assessments are likely to be required.' If shortcomings are detected they have to be notified to the BSI along with an improvement plan. The BSI has extensive information- and access rights to verify compliance with legal requirements – this includes demanding proof of implementation and, if a lack of IT security measures is determined, it can also impose fines.

The situation is always difficult when failings cannot be resolved for financial reasons. The German federal states are liable to fund the investment costs. However: 'For a number of years we have been following the case of a hospital which had to move its computer centre into a building with pressurised water pipes under the ceiling,' Holzbrecher-Morys reports. 'The state should have paid for the replacement of the pipes, which are clearly a flaw, but for years it has not done so. In this case, the hospital's hands are tied, the problem continues but the BSI cannot do anything about it.'

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Costs can equate to an entire annual budget

The DKG does not deny that the implementation of the measures detailed in B3S is associated with costs. On average, they translate into a one-off investment of €2 million, with an annual €600,000 for operation, staff and investment costs in the following years, according to a current survey. 'For some hospitals, this equates to their entire annual IT budget,' Holzbrecher-Morys points out. 'But, we have no satisfactory answers as to how this should be covered. Without some financial leeway it is difficult for some hospitals.'

However, he maintains that the improvement of IT security is necessary for all hospitals, including those with fewer than 30,000 cases a year. 'An IT security breach can quickly turn into a data security breach. Even more important: IT security also means patient security. All hospitals have responsibility towards their patients, which is why they must focus on this subject.' This is also the view at the BSI, which stated: 'Information security is the prerequisite for successful digitisation of IT-security. IT security is not a cost item but a necessary investment into operability and the future of an organisation. It should become routine in the same way as disinfection.'

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To make it easier for smaller institutions, the DKG is currently working on a 'light version' of the B3S, which makes it possible to achieve a lot with low expenditure: 'IT security must be internalised,' Holzbrecher-Morys explains. Initially an IT security officer is appointed. Additionally, all staff members should receive regular training on the subject. These are some essential points.'

est providers usually are awarded the contract without employees' competence being checked. The good news: physicians, at least in Germany, tend to be more reluctant to prescribe antibiotics. In Germany, 25 percent of all patients receive antibiotics, in southern European countries the rate is twice that number – 55 percent in Greece, for example, Popp points out. With increasing migration, infection control has become an international issue. While MRSA is retreating, the non-resistant variant of this bacterium causes thousands of deaths each year, according to a German Society for Infectiology report. In Germany, there are 400,000 to 600,000 treatment-associated infections each year, 10-15,000 of which are fatal. They are connected with hospital and non-hospital care as the Federal Ministry of Health has explained on its website since 2015. However, one third of these infections could be prevented with hygiene protocols, including measures such as appropriate equipment sterilisation.

Well-meant programmes from ABS to APS

'Since the "Microbial Threat" conference, held in Copenhagen in 1998, the 2001 EU report on "Prudent Use of Antimicrobial Agents in Human Medicine", so-called Antibiotic Stewardship (ABS) Programmes are considered necessary to rein in antibiotic resistance by rational anti-infection protocols. ABS programmes have proved to influence resistance, costs and use positively, and have become an important component of patient safety in modern healthcare,' the ABS Initiative's website states.

Popp begs to differ. In his opinion, first there is no sufficient data pool on the administration of antibiotics in hospitals. Secondly, he claims, 'ABS doesn't work, since the freshly certified ABS experts, once they do exist in a hospital, don't have time for education and recommendations.'

Johanna Knüppel agrees. 'The main task of hygiene experts in nursing is handling the hygiene plan – which is nothing but a fig leaf anyway.'

The Aktionsbündnis Patientensicherheit e.V. (APS), an initiative founded in 2005 to focus on patient safety, is optimistic, since its first international day of patient safety was held with WHO support: 'APS will continue to point out the issues that obstruct safe patient care.'

To make a long story short: Improvements, or even solutions to the hygiene problem, are not in sight even though everyone is busy working on them.

And politics? In the political arena, cynics would say, the motto 'only a dead patient is a good patient' appears to prevail. The ones still alive need to try to be well informed and prepare themselves for their hospital stay, for example when surgery is scheduled. The best way to begin: Ask your family doctor to screen you for multi-resistant bacteria, try to eradicate them and make your immune system fit for the hospital environment. If you do this, you enter the OR as a 'healthy' person, and your chance of leaving the OR and hospital in the same healthy state increases considerably.

ection

Under cyber attack

What can happen when a cyber attack is successful was demonstrated in July 2019. The entire network of the DRK hospitals in Rhineland-Palatinate and Saarland was hacked. The BSI knows of further cases in hospitals in Neuss, Giessen and Fürstenfeldbruck. 'Most hospitals have numerous IT connections – 30,000 devices is not unusual. Add to this different IT and device suppliers and old systems, no longer supported, and cannot be integrated into modern IT security structures without great difficulty,' which make access easier for hackers. At worst, this unauthorised access not only leads to theft of sensitive patient data, but also to changed or switched off product functionality. Unknown consequences for health, or even patient death, could result.

The current version of the B3S is now being revised. 'It is a document in progress, with continuous revisions,' Holzbrecher-Morys explains. 'We will have finished it in the third or fourth quarter of 2020 and be prepared for the next assessment in 2021. We have succeeded in writing a joint paper with all those involved in the process, which was approved by the BSI, which was not a given. We have made a successful start and now we can build on this.'

Markus Holzbrecher-Morys is Deputy Managing Director of the Department for IT, Data Exchange and eHealth at the German Hospital Federation (DKG). After gaining his IT degree he initially carried out academic research, focusing on further developments of neuroinformatic procedures for bio signal analysis. Since 2008 he has been responsible for electronic data exchange procedures in hospitals and hospital IT at the DKG, particularly for technical data protection, IT risk management and information security.

Sharing concept works for stage IV lung cancer patients

Improved cancer communication

The Heidelberg Thorax Clinic is trialling a newly structured, longitudinal communication concept to meet proactively the complex needs of stage IV lung cancer patients and their relatives. The concept is aimed at enhancing prognostic understanding and building the basis for proactive care planning, early integration of palliative care and shared decision-making, ultimately to improve improving overall care. First experiences look promising. Patients, and those treating them, talk about better patient-doctor relationships and also about the positive impact on the wellbeing of sufferers, along with a reduced psychological impact on staff.

Report: Cornelia Wels-Maug

According to one study, more than 60% of medical errors occur due to lack of communication between doctors and patients.

The German Federal Ministry of Health (BMG) acknowledged the importance of communication for treatment success when it listed 'strengthening patient-centred care/ information for patients' in its 2008 National Cancer Plan as one of the four fields of action to contribute towards improved care of cancer patients.

At the Heidelberg Symposium 'HeiMeKOM Heidelberg Milestone Communication' held in the Thorax Clinic at the end of January, Dr Antonius Helou of the BMG explained that to enhance patient focus, the ministry is examining the relationship between doctors, nurses and patients. Given the importance the BMG places on communication, it also promotes the HeiMeKOM initiative.

The symposium featured insights and experiences gathered in the context of this project so far. The initiative is run by the Thorax Clinic at Heidelberg University Hospital, the Department for General Medicine & Health Services Research and by the Institute for Medical and Pharmaceutical Proficiency Assessment (IMPP).

A ground-breaking concept

The choice of the title 'Milestone Communication' refers to a novel format of interactions with lung cancer patients who have a terminal prognosis (median survival < 12 months). It builds on the four central discussions, or milestones:

- the initial discussion
- discussion of the treatment concept
- discussion of perspectives
- discussion around censensus

With this new concept, a nurse is now always present alongside the doctor during these discussions, with the treatment team having received special communication training. Nurses also call patients a week after each milestone discussion and then monthly, to assess their understanding and progress of the illness and their needs for palliative care, making the care process as seamless as possible.

HeiMeKOM also aims to enhance interprofessional cooperation and assist all those involved in the treatment process in supporting one another during these challenging discussions.

For the first time: recording patients' preferences

Keeping records that also integrate relatives is done to ensure patients are better listened to and that sensitive topics (the importance of therapeutic measures with limited effect, proactive care planning and palliative care) are integrated into the care plan in time and in a more structured manner and then successfully implemented.


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The exchange with the patient during more stable phases of their illness is particularly important, especially as the target group consists of people with limited life expectancy. Great importance is attached to their wellbeing and to maintain, or respectively improve, the quality of their lives. Patients are now also asked about their preferences, with those being documented.

What has emerged is patients' wish for continuity, for regular appointments, for reassurance that the treatment concept is the right one and for opportunities to talk about their end of life care.

The HeiMeKOM concept also has been recognised outside the Thorax Clinic and was awarded the 'Springer Medicine Innovation Prize 2019 – Inter-professional Projects in Healthcare', at the 7th Interprofessional Healthcare Congress.

HeiMeKOM in action

Some advanced stage lung cancer patients at the Thorax Clinic have been cared for using this approach since May 2018. The key objective is to improve care helped by the new approach and to generate evidence for it. A range of qualitative and quantitative tools is available for evaluation, including assessments of patients' needs for support and quality of life as well as health economic measures of captured via interviews, workshops and questionnaires.

The first (133) and second (172) milestone discussions along with follow-up conversations (total: 146) have been evaluated so far. The assessment of the other two milestone discussions, as well as the control group discussions, have not been concluded yet, so the final results of the project are not available.

The treatment team at the Thorax Clinic has received a lot of positive feedback from patients and colleagues, confirming the high rate of acceptance for the project.

Initial findings

The evaluation of the milestone discussions indicates the following positive effects:

- Improved individual quality of life for patients & relatives
- Less distress amongst patients & relatives
- Better orientation in the healthcare system, incl. improved cross-sector networking
- Enhanced informed decision-making: better adherence to treatment, higher prognostic awareness, more efficient use of healthcare resources (fewer A&E admissions at night and during weekends)
- Strengthening of patient competence
- Enhanced interprofessional cooperation and team processes
- Improved communicative competence within the treatment team.

Compared to the quarterly costs incurred for a cancer patient's pharmacological care, the cost of medical consultations carries hardly any weight. A staff member at the Thorax Clinic calculated that the quarterly cost of medication is around €20,000 while medical consultations amount to between €80 and €150.

This is a good reason to continue with HeiMeKOM, to extend it to other conditions and to embed the milestone concept in standard care in the medium term, so that more patients can benefit from it.

'HeiMeKOM should cover the entire medical landscape,' says Professor Michael Thomas MD, who is the Senior Consultant for Medical Oncology in the Heidelberg Thorax Clinic. Undoubtedly, the professor will not be the only one to wish for this.

Potential effects of digital health technology

Watched by an angel or Big Brother?

Report: Mark Nicholls

Cardiologist Professor Martin Cowie raised an important issue during a session to examine the challenges of the Digital Cardiovascular Health Revolution, held at the European Society of Cardiology Congress 2019 in Paris. In his presentation 'Future impact of digital health on patients – guardian angel or Big Brother?', he confirmed that, within digital health transformation, the role of physician and the patient-doctor relationship will continue.

However, this, he said, will change over time and it is crucial for doctors – and cardiologists – to fully engage in discussion to help shape the future of digital healthcare.

GP access 24/7

Cowie pointed to the Babylon Health App, with which NHS patients in the UK can leave their GP surgery and sign up to the app to gain GP access 24/7 – although chronic conditions, mental health and pregnancy are not covered. 35,000 NHS patients have already signed up, he noted.

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As Professor of Cardiology at the National Heart and Lung Institute, Imperial College London – and chair of the ESC digital health committee – he said cardiologists will still need to interact with patients to conduct complex procedures. However, he foresaw where much of the preparation – such as the imagery in advance – may be conducted remotely.

He also warned of dangers that technology, while flagging up a potential minor problem, might cause anxiety rather than reassurance in a patient and result in them going to hospital anyway to get checked over. 'That is a case of technology driving healthcare in the wrong direction,' he observed. 'It's about using it where it can demonstrate value. I do believe we will get there, but it's not going to be straightforward; we want evidence of the benefits – show us it's useful and we may adopt it.' However, he added: 'Twenty years from now, we will not be talking about digital health, all healthcare will be digitally supported.'

Digital health polarises

Opinions on digital health applications remain polarised among physicians, underlining the need for doctors – and the ESC – to be involved in the discussion.

'The medical profession has to ensure it is appropriately and strongly involved in the digital health transformation,' Cowie added.

'How do we translate data into better outcomes? It's not about using more data to make more decisions but about using data to make better decisions.' As to whether digitisation is a guardian angel, or 'Big Brother', he suggested this question still has to be answered.

During the ESC session on the Digital Cardiovascular Health Revolution, other topics explored included whether the workforce was ready for such changes made by digital healthcare; its impact on physicians; the value of wearable devices and monitors; and their role in cardiovascular disease prevention and treatment.

Martin Cowie is Professor of Cardiology at the National Heart and Lung Institute, Imperial College London and an Honorary Consultant Cardiologist at the Royal Brompton and Harefield NHS Foundation Trust. He is also chair of the ESC digital health committee. His major clinical and research interests are in health technology assessment and the delivery of efficient and effective care for patients with heart failure, with a particular focus on new technologies: diagnostics, drugs or devices.

Reducing healthcare costs even though optimising patient care

Remote monitoring technology advances

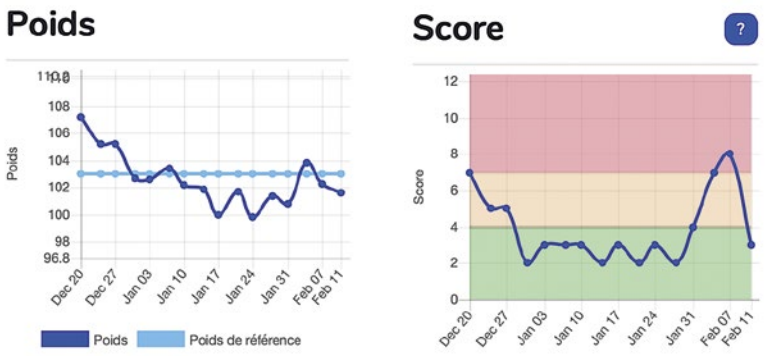
Report: Jane MacDougall

The remote patient monitoring technology and devices market has attracted significant investment in the past decade and is growing at an extraordinary rate. Expected to reach around 28 billion euros by the end of 2023, this market is very attractive to many big name companies that want to be 'connected' such as Qualcomm Life, Inc., OSI Systems, Inc., Philips Healthcare, Abbott Laboratories and GE Healthcare among others. The promise of reduced healthcare costs while maintaining, or even advancing optimal patient care, being too good to resist.

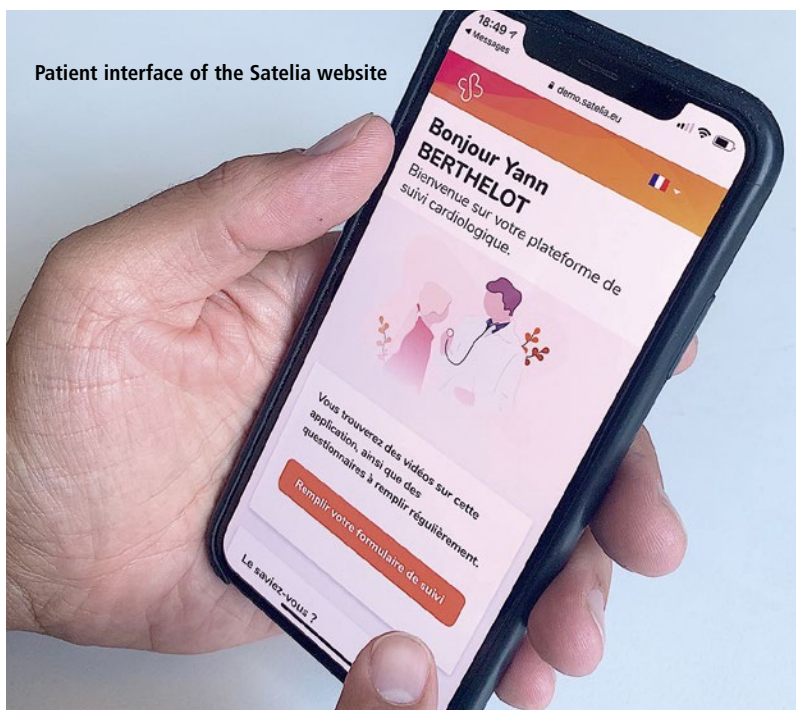
Just how realistic this is and how many healthcare professionals, hospitals and patients are actually using such devices and systems successfully long-term and how much is being saved after initial set up costs is debatable.

3.9 million CVD-related deaths in Europe

Cardiovascular disease (CVD) is the major cause of death for men and women in many European countries. Annually, 3.9 million CVD-related deaths are recorded in Europe – with over 1.8 million in the EU, where, in 2015, around 6.1 million new CVD cases were diagnosed. This means at least 49 million people are living with CVD in the EU alone.



Satelia-control centre HCP Side weightrisk score



Patient interface of the Satelia website

Due partly to lack of awareness in the general population and low rates of diagnosis, these figures are probably underestimated. The absolute number of cases is increasing due to three main factors; poor lifestyle (smoking, obesity, diabetes, lack of exercise), better detection of disease and ageing populations.

The University Hospital Centre (CHU) in Bordeaux, France, realised that a single aspect of CVD, cardiac failure (HF), was seen to account for more than one billion euros expenditure a year, more than 60% of their total budget on hospitalisation for these patients alone. In 2018, Dr Nicolas Pages, a junior hospital doctor in the CHU-Bordeaux was approached by the hospital's cardiologists for help in reducing this extraordinary burden on their service. Why? Because in 2017, Pages had created the digital start-up Satelia, built on a simple web-based premise. He had shown with a software developer, that it was possible to improve post-operative follow-up of out-patients and reduce associated costs by a simple, user-friendly system.

In this first case, their methodology was based on data gathering by directly interrogating patients to enrich algorithms on post-operative pain. In this way they had, by predictive diagnosis and adjusting prescriptions to individual needs, been able to improve the care for this patient group. And so, the idea of Satelia Cardiologie was born.

The online-based tool relies on patients entering the system at their primary consultation with the cardiologist. Within a matter of minutes they are registered in the system with a remote connection via their mobile phones or home computers. There is no need to download an application and no special remote monitoring device is required. After the consultation, the patient is sent messages via SMS at the frequency the cardiologist feels is necessary, perhaps once a week, perhaps several times. The messages ask the patient to log-on to the site to fill in a simple questionnaire. Questions are related their symptoms, whether they are out of breath, coughing, more or less tired, have put on weight etc. Fed into constantly updating algorithms, these data help the cardiologist to assess the patient's risk level and the need for further consultation, treatment alterations, or an operation. In this way, out-patient appointments are freed up by extending the intervals to see patients whose health is good and disease well-managed, and so allow patients with poorer health, or new patients, to be monitored more closely or to enter the care pathway, respectively.

Online Access

Patients can also access information online about post-operative care and general health from videos specifically targeted to them, based on their questionnaire replies. For those not connected (HF patients tend to be older and therefore some do not have internet access), a nurse will telephone them and fill in the questionnaire for them so that the cardiologist can still follow them remotely and adjust their care accordingly. Since the May 2018 adoption of this system in Bordeaux, admissions for these patients has reduced by 30%.

Designed for simplicity, the system is constantly under development. Pages thinks modifications are requested about 40 times a week, as doctors use and adapt the system. But this doesn't deter him because it is a clear sign that cardiologists are using the system and seeing where a tweak here or there

Transforming a raw histology image into a spatial roadmap

Deep learning for small cohorts

To investigate rare diseases, applying image-based analytics approaches, including the use of deep learning convolutional neural networks (DL-CNNs), can be a major challenge due to great difficulties in acquiring sufficient numbers of cases and associated digital image sets from the small cohorts typically available. To realise algorithms that are both effective and generalisable, conventional DL-CNN algorithms typically require hundreds to thousands of cases and larger yet numbers of image tile ensembles. In the case of uncommon or rare diagnostic entities, such as encountered in the routine practice of pathology, this data shortfall can be an obstacle. However, Professor Ulysses Balis believes that the use of a particular type of data augmentation technique, as a pre-processing stage to subsequent DL-CNN use, could hold the key and offer a solution to the challenge posed by smaller cohort sizes.

Speaking at the 6th Digital Pathology & AI Congress in London last December, he advocates the use of VIPR (Validated Identification of Pre-screened Regions), a particular type of spatial data augmentation technique which transforms an image's raw pixels into a local kernel figure-of-merit heat map.

When used as a pre-processing step to subsequent use of DL-CNN approaches, his group has observed that the resulting ensemble-based algorithm can converge to a robust image classification and segmentation solution with far fewer cases and images, than encountered with use of DL-CNNs alone.

This combination can provide a workable approach matching the diagnostic cohort sizes as encountered in histopathological entities.

Balis explained how the VIPR-based data augmentation technique spatially prequalifies image regions with a supervised figure of merit, allowing for subsequent deep learning pipeline stages to benefit from enhanced foreground delineation.

This image augmentation approach uses an initial set of prototypic local image kernels as the starting point for their subsequent equivalence testing throughout the entire surface are of image sets under interrogation, ultimately yielding a pixel-level heat map indicating all areas that are similar (from textural, luminance and colorimetric aspects) to the initial search predicate(s).

Use of VIPR allows thousands of training images to be reduced to hundreds or even tens, and Balis suggests that, by use of VIPR-based heat maps as an intermediary synthetic image, satisfactory performance from DL-CNNs, including their exhibiting of more rapid algorithm convergence, can be realised on the small image sets that pathology routinely encounters.

'It's effective for rare entities where only small cohorts of images or ROIs are available,' he added. 'It potentially allows pathologists to operate at their highest credentialed level of practice, given the interactive, real-time nature of the tool, which operates in the spatial domain with an intuitive, exemplar-driven model.'

During his presentation 'Augmented Deep-Learning Pipelines with Use of the VIPR Algorithm to Realise Histology Image Segmentation/Classification in the Setting of Smaller Training Image Sets,' Balis explained: 'If you have a small cohort of cases, you have the challenge of having the algorithm converge upon a generalised solution.

'Many contemporary AI approaches that address image classification make use of some variant of deep learning, but deep learning typically requires many images or image tiles to allow for convergence upon a robust and generalisable solution.'

With many diagnostic entities in pathology offering case cohort sizes that are too small in number to qualify for direct application of deep learning techniques alone, Balis believes the use of a pre-processing stage at the pixel level – with VIPR being one such example will help overcome that.

He feels that image data augmentation techniques, in general, and VIPR specifically, can serve as the vehicle by which smaller numbers of images can be suitably magnified in their representational content of foreground subject matter of interest, as a means of extending the stochastic likelihood that a DL-CNN-based classifier will recognise the intended features of interest.

VIPR's role

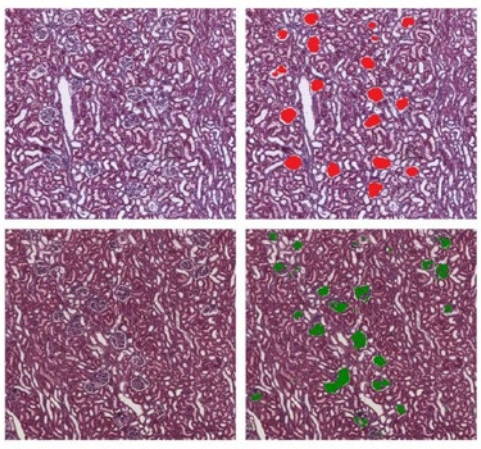
This approach effectively shifts deep learning's unsupervised learning mode to a supervised learning mode, but without the typically associated heavy burden of manually generating hand-drawn ground truth segmentation maps. 'That's VIPR's role,' he said, adding: 'We can transform a raw histology image into a spatial roadmap where individual pixels are transformed from merely conveying local luminance information, to their representing a local domain goodness-of-fit for one or more bespoke image features, thus realising a powerful image pre-processing step.'

In 97% of instances tested so far (over 850 predicates), he said VIPR will converge on a solution with AUC >0.90, with fewer than 10 vectors. 'This overall approach appears to exhibit robust performance, even for novel and cognitively challenging annotation exercises, and even in the setting of small cohorts of cases and image set sizes,' Balis said.

'Deep learning pipelines with pre-processing steps purposefully designed to operate within the constraints of the known small cohort sizes of histopathology entities are compelling, in that they can offer the possibility of [algorithm] classification convergence in more instances than with the use of deep learning approaches alone.' (mn)

Ulysses Balis is Professor of Pathology and Director of the Division of Pathology Informatics at the University of Michigan. His long-standing interest lies in the intersection of engineering, computational approaches and the practice of medicine. He has research interests in several areas of pathology and medical informatics including machine learning and the use of encoded data, image-based analytics, machine vision tools for histopathology and image-based search algorithms.

Exemplar: Automated Glomerulus Identification

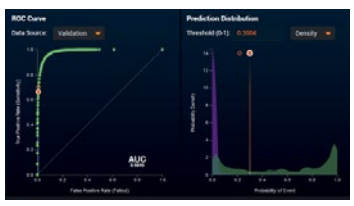


Model system: use of VIPR, Markov Models, and Gradient Descent Support Vector Machines with an ensemble of 68 Vectors

Vector selectors were chosen to match ground truth maps (regions in red) provided by a subject matter expert, yielding the generation of a fully-automated computational pipeline that can identify both intact and fractional sections of glomeruli (in green), from novel, cross-validation images that were not previously used for training.

Classification convergence was obtained with 41 fields of view from 12 cases, yielding an AUC of 0.9840.

This trajectory of convergence exceeds performance typically encountered with the use of conventional DL-based Convolutional Neural Networks alone, When so few training tiles are used.



Nicolas Pages MD, a graduate from Bordeaux University, also specialised in emergency anaesthetics, intensive care recovery and paediatric anaesthetics. Currently he works as a medical resident at the Bordeaux University Hospital Centre (CHU). He co-founded Satelia in 2017 and is actively involved in its evolution and development.

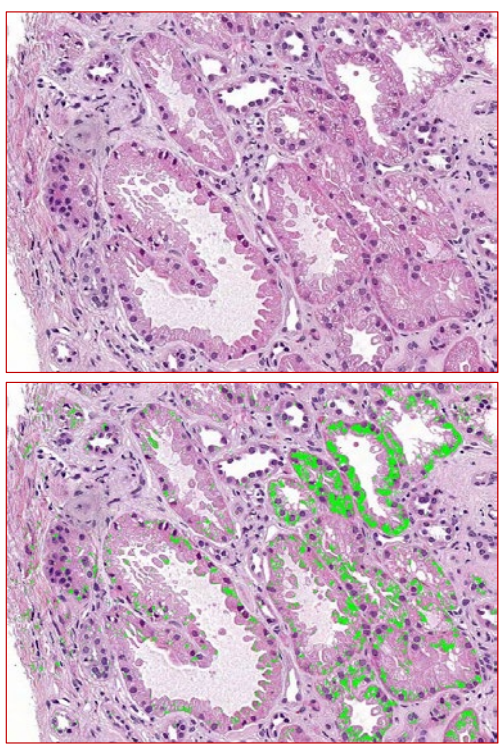
can make it more accessible and pertinent to their and their patients' needs.

Uptake of the system has been strongly aided by its prescription being 100% reimbursed by social security and by the fact that doctors are at the centre of its development.

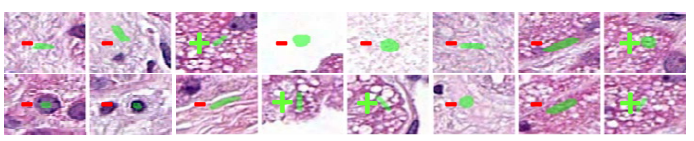
Today, Satelia has 21 employees; including two data scientists and four developers and is ready to expand. Expansion in France has been helped enormously by the reimbursement rate, but Pages also has his sights on Italy and Germany, where he is already working with existing digital platforms that are now licencing Satelia to distribute instead of their own brands, due to its better fit with medical professionals and patients. Satelia, as a concept, can be adapted to remote healthcare anywhere and in any disease.

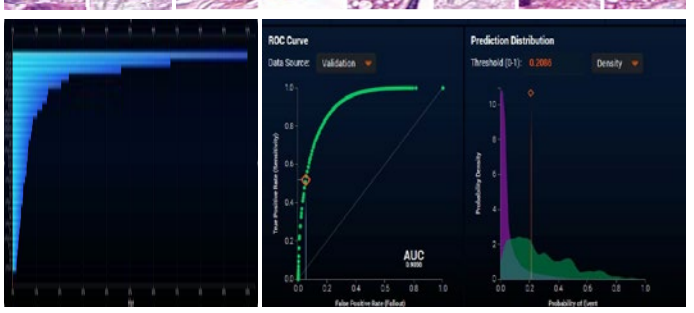
Pages has plans to cover up to 20 different diseases within the next five to six years and is actively seeking partnerships to develop the system internationally. With such an auspicious start, the world of remote medicine does indeed appear to be Satelia's oyster.

Exemplar: Renal Tubule Vacuolization Classifier



- 16 distinct VIPR spatial pre-filters
- Each vector processed through a low-pass Gaussian pipeline to increase spatial distribution of matching events
- Initial AUC of 0.906 / Final AUC of 0.936, maintained with cross-validation
- VIPR vectors (positive and negative) as below:





Heading for personalised medicine

Computational pathology

Computational pathology has increased applications for diagnosis, prediction of prognosis and therapy response, facilitating the movement of healthcare towards personalised medicine.

Report: Mark Nicholls

Coupled with deep learning, such tools are ever more efficient and robust within research and clinical settings. The growing role of computational pathology was highlighted by Professor Andrew Janowczyk at the Digital Pathology and AI congress in London last December.

In his presentation, 'Computational Pathology: Towards Precision Medicine', Janowczyk – an Assistant Research Professor in The Centre of Computational Imaging and Personalised Diagnostics (CCIPD), Case Western Reserve University in Cleveland, Ohio – outlined results from recent research employing digital pathology in the domains of oncology, cardiac care, and nephrology as well as development of user-friendly open-source tools for practitioners.

Computer-aided diagnosis (CAD) – using algorithms to help clinicians analyse clinical data – has become increasingly useful in improving the efficiency and robustness of medical diagnosis because it is fast and reproducible and can leverage vast amounts of data that already exists, Janowczyk explained. Notably, with the increase in the number of digital slide scanners, more data is being created daily, at an ever-increasing rate, further fuelling these approaches.

This data, he said, can be used to perform data mining to identify trends; identify subtle image patterns which may not be visually discernible; and build systems to aid – not replace – doctors through decision support.

'This will not put pathologists out of business,' he stressed, 'but will transition them to a different type of more integrative work.'

CAD can be divided into clinical applications and research, Janowczyk pointed out.

Clinical applications include the ability to recapitulate and automate existing processes; support cancer detection, grading, counting and area estimation tasks; deliver improvements through quantification and reproducibility, and disease definitions, and help with visual confirmation.

For research, algorithms can be used to develop novel features and metrics enabling: sub-type discovery, biological elucidation, and deliver improvements through augmenting current clinical knowledge via new insights. However, he suggested that CAD research and clinical applications are separated by at least a decade.

He used breast cancer risk recurrence score as an example. With a 21-panel gene-expression assay, costing $4,600 a test, taking two weeks to complete and resulting in tissue destruction, he compared that with an image-based risk score based on routine slides that would be expected to cost two orders of magnitude less, be available within minutes, performed locally and be non-tissue destructive.

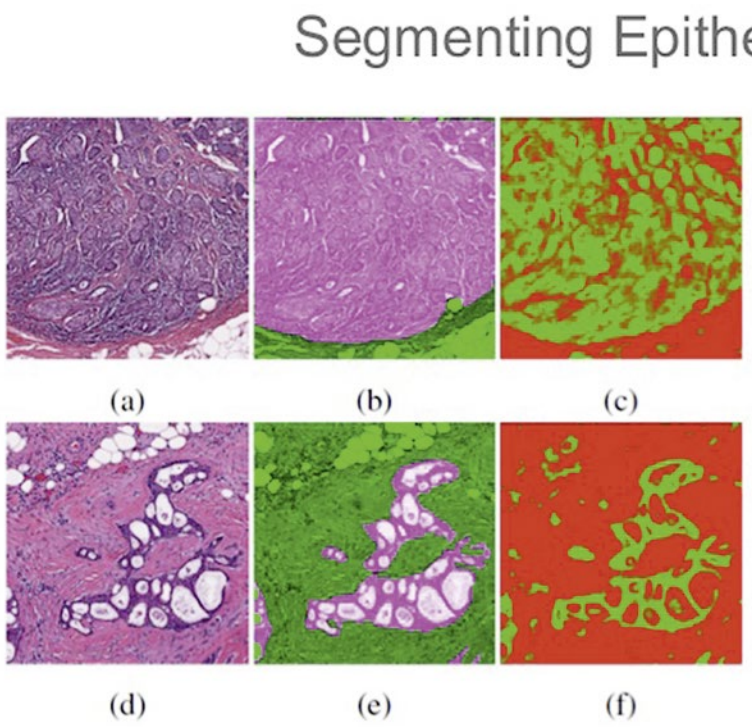
This is realistic, Janowczyk suggested, given that the individual components of the current clinical grading scheme (Nottingham histologic score) are already prognostic and the increased precision afforded by leveraging computation algorithms will only add to their performance.

There are a number of reasons, he added, to use deep learning because it is significantly faster to implement compared to the development of hand-crafted features, and shows 'great robustness' because it can examine more cases than a typical developer could.

With deep learning, the robustness of many common image analysis tasks in digital pathology (e.g. cell counting, area estimation) is greatly improved.

Creating algorithms that perform well can carry out labour and time intensive tasks for which the pathologist manpower is not available to do (e.g. segmenting individual epithelial regions). In addition, algorithms may be able to identify and validate patterns which humans are not capable of quantifying easily, such as slight differences in textures or morphologies.

However, he acknowledged that CAD is patient-based and thus it can take years to find patients with rare diseases. Janowczyk also stressed that improved experimental design,



Original images in (a) and (d) with their associated ground truth in (b) and (e) overlaid in fuchsia. We can see that the results from the deep learning, in (c) and (f), that a pixel level metric is perhaps not ultimately suited to quantify this task as DL is better able to provide a pixel level classification, intractable for a human expert to parallel.

Telepathology service to reach across eastern Canada

Spreading quality pathology

Following success of telepathology in the eastern region of Quebec, the service is set to be further expanded across its remote areas. There are also moves towards a fully digital service at some sites, to introduce tele-autopsy into remote regions and extend the geographical coverage further across the region.

The latest developments were outlined at the Digital Pathology and AI Congress in London by Dr Olivier Michaud, anatomic-pathology resident at the Université Laval, Canada, in his presentation 'The Eastern Quebec Telepathology Network: Eight years of improved quality pathology services in remote regions.'

This network was created in 2004 through public funding and implemented in 2011 in 20 sites, to provide access to diagnostic telepathology services to a population of 1.73 million people dispersed over 452,000/km². The main objectives were to provide pathology coverage in the Eastern Quebec territory and bring patient-centred pathology closer to communities. Prior to that, a lack of pathology services often led to delays in surgery, two-step surgeries, and patients being transferred long-distance. There were also difficulties in recruiting pathologists.

'In some departments there was only a part-time pathologist, or none at all, and the schedule of operations was dependent on the availability of a pathologist,' Michaud said. 'From a pathologist's perspective, there was insecurity in working alone, especially in early practice. It was impossible to rapidly obtain a second opinion and with immunochemistry performed in university hospitals, there were delays in getting the slides back.'

The telepathology network was established with several key objectives: to prevent interruption of frozen section service in laboratories with no pathologist on site; to prevent two-stage surgeries and patient transfers; to facilitate recruitment and retention of surgeons and pathologists in remote hospitals, and to reduce professional isolation and insecurity among pathologists who work alone.

In Eastern Quebec, 24 sites with seven hospitals are without a pathology laboratory, 17 with a laboratory, five with no pathologist, five with one pathologist and seven with two or more pathologists. 'It's a decentralised network,' he said, 'so not all consultations go back to Quebec City.'

The network now enables expert opinion, intra-operational consultations, urgent biopsies, neuropathology, macroscopy supervision and has a tele-autopsy capability.

Each site is equipped with a macroscopy station, video conferencing devices, a drawing tablet, and a digital whole slide scanner with images saved on a dedicated telepathology server.

The macroscopy station and video conferencing device allow the pathologist to interact with the surgeon and once the selection of the sample is completed, a technician proceeds to cryo-sectioning and staining. 'The slide is scanned and sent to receiving centre for analysis by the pathologist,' Michaud explained. Using designated software, the pathologist can read the clinical information, examine whole slide images and also dictate or type a final report.

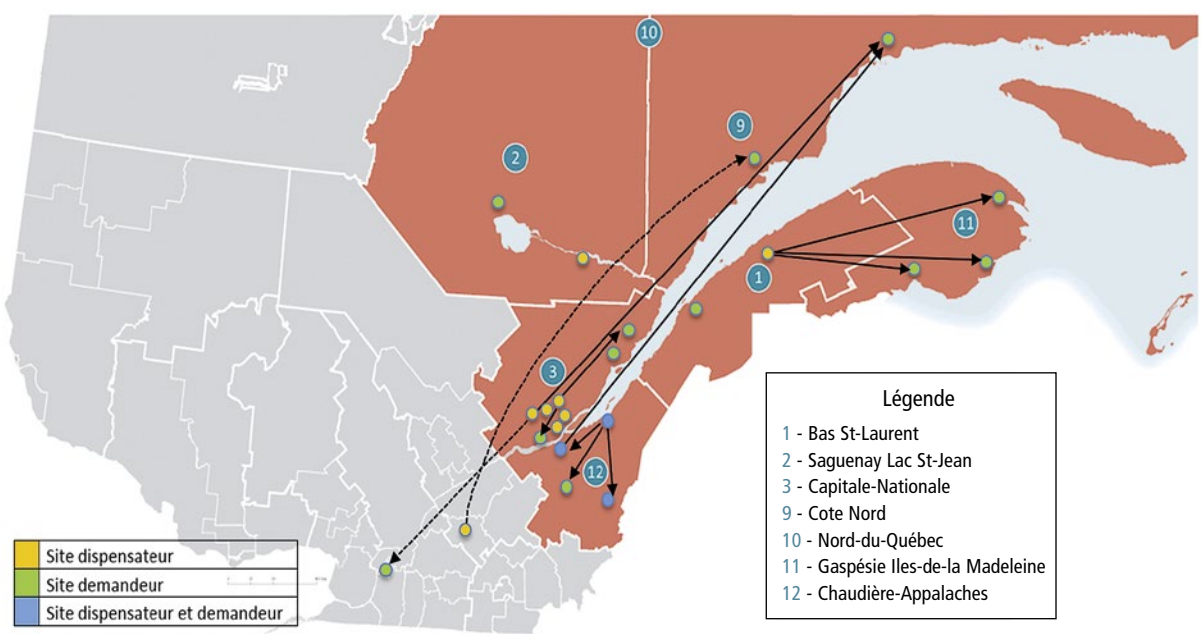
Macroscopic supervision covers colectomies, hysterectomy, mastectomy, salpingo-oophorectomy, thyroid and parathyroid, lung lobectomy, dermatopathology excision for melanoma, other gastro-intestinal resections and genitourinary work.

In an average month, the network saw 164 slides scanned for primary diagnosis (including urgent interpretation) and with a maximum of 792; 39 for intraoperative consultations; 49 for expert opinions between pathologists, 35 for assistance to macroscopic description, with 631 slides scanned for teaching purposes.

Michaud added that the workload is outside the normal caseload and usual practice of the pathologist.

When sent for expert opinion, the average turnaround time was 32 hours, with 38.5% completed in 12 hours. With frozen sections, 98.1% were concordant and average turnaround time was 20 minutes, compared to 15 minutes when a pathologist was on site before.

Michaud explained that the service had proved successful with the key objectives achieved: interruption of frozen sections were prevented, there was a reduction in two-stage surgeries and patient transfers, recruitment and retention issues were improved, and pro-



Dr Andrew Janowczyk is an Assistant Research Professor at the Centre of Computational Imaging and Personalised Diagnostics at Case Western Reserve University, and a senior research scientist in the Department of Personalised Oncology at CHUV (Switzerland). He is also a Senior Bioinformatician with the Swiss Institute of Bioinformatics. His research focuses on applying machine learning and computer visions algorithms to digital pathology images for disease detection, and the prediction of prognosis and therapy response.

and thorough validation will be needed with new generation tools, because concerns raised by the black-box nature of deep learning are warranted.

Finally, he focused on tools produced by the CCIPD to support precision medicine advances. These open-source tools include the HistoQC, which addresses the unmet need for quality control by identifying and visualising slides of poor quality, thus enabling them to be recut and rescanned immediately before getting into a workflow to a pathologist.

He added that HistoAnno, a tool which employs deep learning-based active learning for rapid annotation generation, is expected to be released in early 2020.

Olivier Michaud is a chief resident for the Anatomic Pathology Training Program at Université Laval, in Quebec City, Canada. His main research focuses on digital pathology implementation in public funded systems, as well as in breast pathology and the implementation of new targeted therapies in breast cancer treatment.

fessional isolation and insecurity among pathologists reduced.

However, Michaud acknowledged that challenges and barriers remain, with surgeons having to adjust to asking for the service, different work patterns, and the need for mutual confidence and trust between centres and personnel. There was also the need to adapt workflow, archiving, integration with local LIS, issues of prioritising telepathology over in-house cases and reimbursement and also legal issues to be resolved.

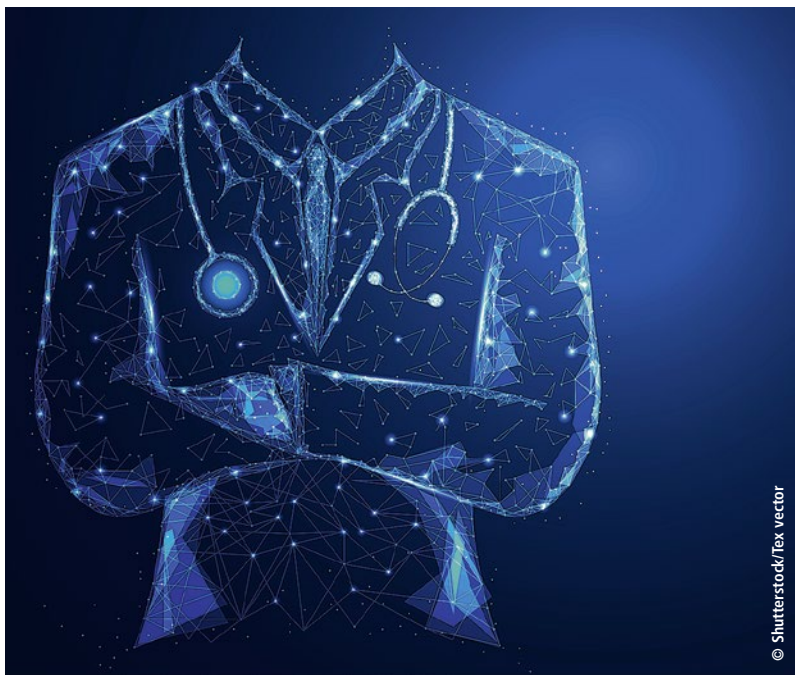
Yet, there are now plans to expand to other regions in Quebec and fully digitise laboratories at selected sites. 'We are looking at tele-autopsy for remote regions,' he pointed out, 'so the body does not have to be transported to Quebec – and we are already doing that for educational purposes.'

(mn)

Lab technology on a square centimetre

Self-testing health in space

Nanoelectronics and digital technologies R&D and innovation hub Imec recently received NASA funding to test a new technology in a gravity-free environment. Eventually, this will enable astronauts to perform blood tests to monitor their health. We discussed the project and technology with Nicolas Vergauwe, CEO of miDiagnostics, the Leuven firm that developed the diagnostic device, and Susana B Zanello, Development Manager at Imec's design centre in Kissimmee (Florida) and also the project's principal investigator.



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Report: Madeleine van de Wouw

Vergauwe: 'The operating principle of the device is based on capillarity – the same force that sucks spilled coffee into a napkin or tissue.

'This enables the technology to be fit in very small devices. The silicon chip is as big as the chip in a smartphone. It is integrated in a test card the size of half a bank card and a device the size of a bank's ID-card reader. An additional advantage is the low cost of the test card, which is for single use.'

Applications from chemotherapy monitoring to coronavirus screening

'Usually, blood analysis takes at least a day because the blood must be examined in a laboratory. Since the information is not available during a consultation, doctors will often prescribe antibiotics to a patient with a possible viral or bacterial infection – this often turns out to be unjustified. Our device enables blood analysis during the consultation, so infections can be distinguished without delay and treatment adjusted accordingly.

'It can also be used for patients undergoing chemotherapy. For each new cycle, it must first be assessed whether the body has recovered sufficiently. The actual therapy can often be done at home, but for the blood test, patients need to go to hospital. 'With our device, the blood test can also be performed at home. We can roll it out even further and apply it at airports, for example. Look at the current situation with the coronavirus. 'You can screen people by measuring temperature, but there can be many reasons for having a higher temperature. With our device, you could specifically check for the presence of the virus.'

Another application is use in countries where healthcare is not readily available. 'I was in Sierra Leone during the Ebola outbreak. We had to build a whole infrastructure with our Western instruments. If we could provide diagnostic tools of this kind there, people on the spot can take the initiative and start treatment themselves.'

Using a needle, a few drops of blood are applied to a test card, which will be inserted into a device. Many existing rapid tests are based on the detection of antigens of a specific virus or bacterium. They are easy to use, however, only one specific pathogen is tested.

The miDiagnostics device, on the other hand, is capable of detecting various pathogens, such as bacteria or viruses, with one drop of blood, and thus offers a syndromic panel test.

Dr Susana Zanello has 25 years' experience in biomedical research and 12 years supporting human spaceflight research. Her investigations have focused on human health risks associated with space exploration and on the pursuit of solutions for space medicine needs. She recently joined Imec USA as R&D Manager for Space Health.

The physician's role remains

The doctor retains the leading role in diagnostics. A patient who has to undergo a new chemotherapy course, and tests his blood count, does not decide for himself whether he is capable of doing so.

The blood sampling is done with a separately supplied syringe because fitting it would make the device an invasive product, with the necessary regulatory consequences: 'Compare the test procedure with the way diabetes patients tests themselves,' Vergauwe advises. 'The device makes it possible to perform a full blood count, results of which can be read by a doctor on site within 15-20 minutes. The results can also be made available to doctors online. This will of course have to be done via a secure connection.

'The future might bring even further applications, for example via a smartphone, or a reader via Bluetooth to the cloud,' Vergauwe suggests.

Bioscience engineer **Nicolas Vergauwe** joined molecular diagnostics firm Biocartis in 2012 after gaining his PhD at the Katholieke Universiteit Leuven, Belgium, in collaboration with the École Polytechnique Fédérale de Lausanne (EPFL) at Lausanne, Switzerland. He served as the company's Vice President for Innovations, responsible for bringing novel technologies and assay concepts to the market. In 2018, he became CEO of miDiagnostics.

In space

Because capillary forces overcome gravity, NASA sees enormous potential for application in space. Imec received a grant from NASA to use miDiagnostics' technology as a first test in a zero-gravity environment. During parabolic test flights, a team consisting of Imec and miDiagnostic will check the operation of the test cards combined with microgravity to evaluate the correct functioning and robustness of the subcomponents.

Susana Zanello comments: 'This technology demonstration is intended to meet NASA's need for technologies that support human exploration and further commercial activities, both in orbit and beyond. Human exploration in deep space, such as travel to Mars, requires the development of medical devices and the diagnostics of small mass, volume and power requirements, designed for a more autonomous practice of medicine.'

What will the future probably deliver?

miDiagnostics hopes to market the device for use within three to four years. Tests are carried out in collaboration with universities, such as John Hopkins, to ensure sufficient sensitivity and specificity of the test. This process must then be adapted for each country, which have their own requirements, conditions, and guidelines for approval.

'The first tests were positive and now we are going to develop it further', says Vergauwe. 'We are very excited that our technology has been selected by Imec to demonstrate its operation during parabolic flights.'

Zanello adds, with notable pride: 'This is a very exciting process and a good example of how Imec and miDiagnostics work together to bring diagnostics to the most remote places, both on Earth and in space.'

New and old challenges in laboratory medicine

Seeking an ideal lab life

The Central Laboratory at the Medical University Hanover, Germany, is prepared to handle virtually any clinical chemistry task, from a routine test to the most complex analysis. Equipped with state-of-the-art technology and thanks to a high degree of automation, the team can process more than 3,000 specimens, mostly blood and urine, in a single day. Professor Ralf Lichtinghagen, European Specialist in Laboratory Medicine, and Head Clinician in Hanover, and Dr Martin Christmann, European Specialist in Laboratory Medicine at the Central Lab, in Hanover, explain the challenges a lab of that size is facing today.

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Biologist and clinical chemist **Martin Christmann** works at the Institute for Clinical Chemistry at Hanover Medical School. He is a member of the German Society for Clinical Chemistry and Laboratory Medicine (DGKL).

Professor Ralf Lichtinghagen is Deputy Director of the Institute for Clinical Chemistry and Director of the MTLA-School at Hanover Medical University, Germany. His main research is on the molecular diagnosis of malignant diseases, liver fibrosis, MS and stroke. He is a member of the DGKL.

Report: Daniela Zimmermann

'The German healthcare system poses a very specific problem regarding who is allowed to perform and invoice which tasks in a medical lab,' Professor Ralf Lichtinghagen explains. 'The guidelines on evidence-based medicine (EBM) and the German medical schedule for physicians (GOÄ) prescribe that, under normal circumstances, special lab medical services must be provided personally and invoiced by a laboratory physician, particularly services rendered by a specialist lab in a hospital.

Whilst other non-physician medical specialists, such as clinical chemists or those in human genetics are usually able to provide the same kinds of services, the hospital is not allowed to invoice for the services they render. In view of the scarcity of lab physicians this requirement creates a real problem. 'Currently, hospitals can only invoice certain lab services if they were performed by a laboratory physician,' Lichtinghagen points out. Thus invoicing specialist lab services is a real issue – because it is actually illegal for a physician to place an order for lab services for her- or himself.

The German Society for Laboratory Medicine is exploring possible solutions to this problem. To provide the necessary medical element one idea being discussed is additional training in a master program in laboratory medicine aimed at chemists, biochemists, biologists and comparable professionals. As yet the stakeholders, i.e. the affected professional associations, have failed to agree to recognise the state certification such a program would entail. Lichtinghagen is convinced that a certified program can effectively dissolve the bottleneck because, he believes, 'there are plenty of scientists who are extremely interested in the clinical aspects, such as pathologies and the reading of findings'.

Potential fo savings is overestimated

Labs are faced with another staff-related problem: lab managers' expectation that an additional lab line will allow a significant staff reduction is clearly unrealistic. The new technologies and procedures, which are highly complex, require specially trained teams. Moreover, the extensive range of tasks in a modern lab means that not all staff members can be equally well-versed in all areas. In everyday lab life non-specialist staff thus increasingly dread night and weekend duty because they don't feel sufficiently prepared to bear the responsibility, particularly regarding tasks they do not routinely perform. 'Many team members are far beyond their acceptable stress level, which carries the risk that the entire system collapses,' Lichtinghagen points out.

Martin Christman fills sample tubes into a bulk loader, which automatically sorts and processes them

Ideally, each lab has a core team that is sufficiently large and underwent comprehensive training in all relevant areas. But, with automation being the current buzzword, many decision makers in the labs do not wish to acknowledge that more and better trained staff is needed. Quite the contrary, as Christmann adds, 'further staff reductions are expected'.

The role of artificial intelligence (AI) in the lab

AI is another fashion, permeating all professional symposia. In reality, however, AI as yet has little relevance for the everyday lab workload. This lack of relevance is particularly true, as Christmann points out, for 'AI in the sense of machine learning processes that enable a system to develop by itself based on data or algorithms'.

He does acknowledge AI's potential regarding detection of rare diseases: every clinician is familiar with the standard characteristics of the most frequent diseases in the ER, in endocrinology and paediatrics. However, rare diseases, i.e. those a physician faces perhaps once in twenty years, are not on the mental radar screen. In such a case, the computer can provide the crucial pointer towards a specific disease. 'This is a useful field for AI and would help patients who have run the entire diagnostic gamut without clear results.' Christmann is convinced that, in clinical chemistry and in the lab, there will always be a team of people who are experts in the basics, even if AI could gain ground in the lab.

LOINC as a `common language´

Lab procedures are neither standardised to any meaningful extent, nor is there an organisation that pushes for a common framework, mandatory data and binding criteria. In Germany, the DIMDI (German Institute of Medical Documentation and Information) currently manages standard interfaces, i.e. HL7 to communicate findings and orders and ASTM for communication between devices.

However, the standards are helpful only to a certain degree. The moment a lab has to read and analyse data from different sites, e.g. values established in Hanover and Göttingen, unambiguous allocation is difficult. A specific 'language' such as LOINC (Logical Observation Identifiers Names and Codes) might offer a solution. 'Take the measurement of electrolytes for example. For systems to be able to communicate with each other the value called 'serum sodium' in one lab and 'sodium in serum' in another lab needs to have the same code,' Christmann explains.

The same holds true for the different measuring methods of lab parameters, such as creatinine: enzyme measurement on the one hand, and the Jaffe method on the other, use different reference scales – a fact LOINC would have to consider. In turn, this poses a problem for the patient's electronic health record (EHR), since the laboratory values a GP gets from lab partners are established using methods that are different from those used in a hospital where in-patient samples are processed in a central lab.

The consequence is painful: to exclude possible misinterpretations, the GP data and the hospital data must be entered seperately within the EHR.

Manufacturers now use different colour codes for the probes, but all German labs hope to change this on a set date

ISO standard to harmonise colour codes

A seemingly small item in the lab poses another big challenge: each manufacturer uses different colour codes for their blood collection tube caps, thus creating a major source of error. A new ISO standard aims to harmonise the colours worldwide. In Germany, this caused an uproar: too much work, too problematic, too error-prone. But harmonisation is indeed urgently needed: while there is a cross-check to ascertain that tube content matches the cap colour jive, the use of two different colour codes can throw a spanner in the automated systems. 'Nobody knows how this will end. There were a decision and a recommendation, but it remains to be seen whether they will be implemented.' If Sarstedt, a manufacturer of lab and medical technology devices, can deliver next year, all labs across Germany will change colour codes on a set date. This means all devices that check cap colours need to be reprogrammed.

2-D barcodes still in the pipeline

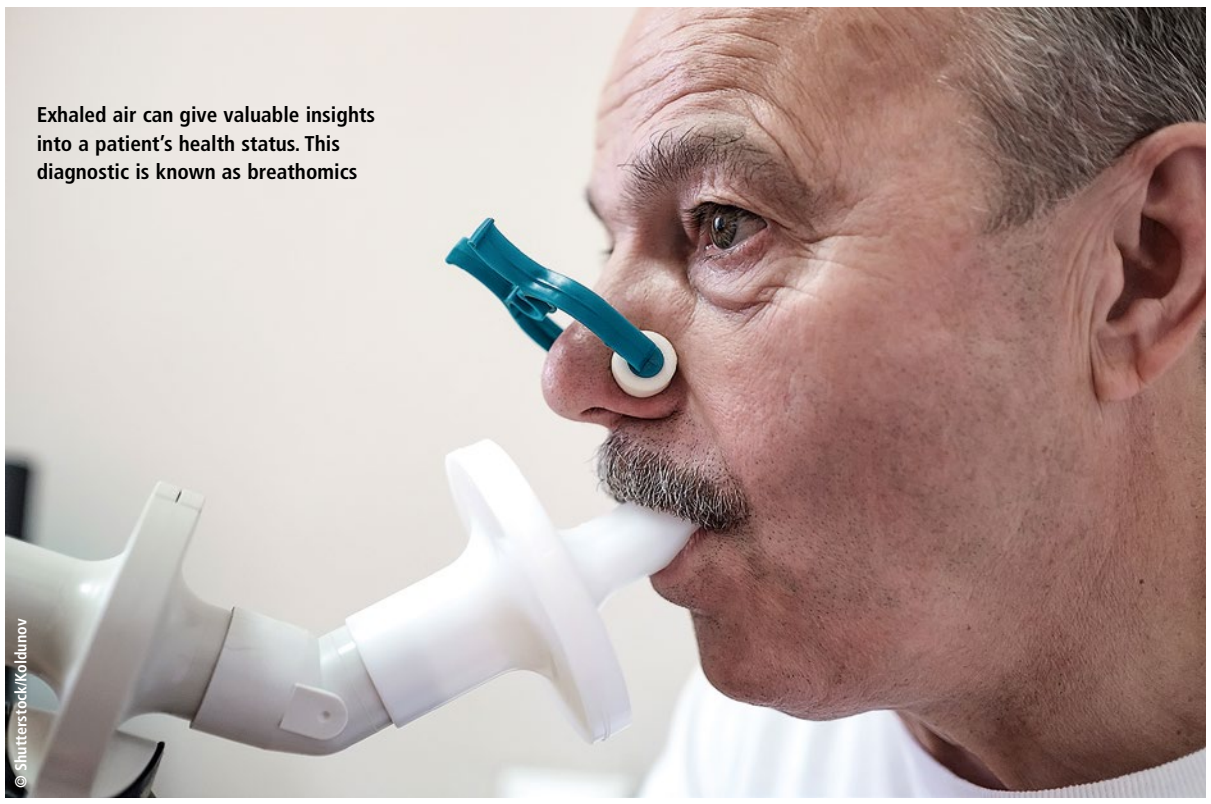
'In pre-analytics peak times 500 to 1,000 samples need to be processed in one hour,' says Lichtinghagen. 'The bulk loader by Sarstedt is the ideal system to handle this volume, since it pre-sorts the samples and automatically places them on the processing track.' To do this manually would be much too time-consuming.

The higher the degree of automation the more important are precisely placed barcodes. If the barcode is wrong or damaged, the system cannot recognize it and the entire process is stopped instantaneously. In order to register the sample it has to pass the barcode scanner – a task that can be done either manually by the lab staff or automatically by the system which also documents the barcode. If the tubes are sent by a pneumatic system, the sample might end up in the inbox without being further processed for hours. Sarstedt is in the process of developing RFID barcodes that are inside the tube and read by sensors. Thus the tubes can be tracked faster and more precisely which will no doubt positively affect sample and analytics quality.

Breath analysis to aid diagnoses

Breathomics: far more than hot air

In diagnostics, it sometimes makes sense to follow your nose. During the Labmed Forum at Medica 2019, Dr Beniam Ghebremedhin and Dr Simona Cristescu discussed the diagnostic potential of breathomics – the analysis of a patient's exhaled air for disease indicators.



Exhaled air can give valuable insights into a patient's health status. This diagnostic is known as breathomics

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Report: Wolfgang Behrends

The idea that a patient's breath can aid in the diagnosis of diseases is far from new: In ancient Greece, physicians considered sweet smelling breath an indicator of diabetes or a fishy smell suggesting a liver condition. While modern breathomics is based on the same principle, it is much more sophisticated and offers a host of diagnostic insights.

Exhaled air consists mainly of nitrogen, oxygen, argon and water. In addition, there are traces of hundreds and even thousands of so-called volatile organic compounds (VOC) – and 'traces' here does mean minute amounts, measured in parts per million (ppm), or even parts per billion (ppb). Nevertheless, these VOCs reflect a person's health status, in certain cases even long before other biomarkers indicate that something is off-kilter.

PD Dr Beniam Ghebremedhin is a specialist in microbiology, virology and infection epidemiology, and a biochemist and specialist in laboratory medicine at Helios University Hospital in Wuppertal, Germany. He also teaches at the University Witten/Herdecke. His research focuses on molecular epidemiology of multi-resistant pathogens, particularly in the hospital, and the development/introduction of new tools for infection diagnostics. His memberships of professional societies include the German Society for Hygiene and Microbiology (DGHM); German Society for Clinical Chemistry and Laboratory Medicine (DGKL); European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and the American Society of Microbiology (ASM).

Prognostic potential

'Changes in the VOC profile of a person have enormous potential for the early diagnosis of diseases and can even be used for prognostic purposes,' said Dr Beniam Ghebremedhin, microbiology expert at Helios University Hospital in Wuppertal, Germany. The major advantage: the method is non-invasive and is thus suited for neonates for whom drawing blood constitutes a risk.

Today, there are several methods to determine VOCs based on mass spectrometry. Gas-chromatography (GC-MS), eNose and infrared spectroscopy have their specific advantages and drawbacks and are suited for different diagnostic profiles. However, there are options beyond lab procedures: dogs can smell diabetes and even lung cancer in the patient's exhaled air.

Unfortunately, as the expert points out, 'Dogs require long and complex training, which makes this option hardly suitable for mass application.'

Extensive preparation, few common denominators

The technical measurements are not straightforward either: the exhaled air samples must be prepared for the instruments to be able to detect VOCs. Several procedures are available, inter alia solid phase microextraction (SPME), thermal desorption or so-called needle-trap techniques, with each of these procedures coming with their own advantages and disadvantages. After the lengthy preparation and processing, the data are analysed to determine the pathology.

Dr Simona Cristescu is Assistant Professor at Radboud University Nijmegen, Netherlands. As a member of the Exhaled Biomarkers Group she studies the composition of organic compounds in breathing air and their significance with regard to diagnostics and treatment monitoring. She is a member of several professional societies, inter alia, European Respiratory Society (ERS) and the International Association of Breath Research (IABR).

Strengths and weaknesses

The numerous procedures cover a wide range of possible diseases. Paradoxically, this strength of breathomics is at the same time one of its weaknesses since, as Ghebremedhin explains, there is currently no standardised approach to allow comparison of results: 'We don't even have an agreed-upon terminology; for example, there is no hard and fast definition for the basic elements such as the different phases of the exhaled air.'

A volatile fingerprint offers a wealth of information

Simona Cristescu, expert member of the Exhaled Biomarkers Group at the Department of Molecular and Laser Physics at Radboud University in Nijmegen, Netherlands, stresses the benefits of a good nose: 'Many diseases follow a specific metabolic schedule. Take a Pseudomonas aeroginosa infection, for example. In the course of the disease, hydrogen cyanide (HCN) and ammonia (NH_3) are produced. Both are volatile compounds of exhaled breath and can be detected. However, the two compounds are not produced at the same time. Thus, if we notice a decrease in the HCN concentration in the exhaled air, and an increase in the NH_3 concentration, we conclude that the infection has entered a new stage and we can adjust the treatment correspondingly.'

In brief: the chemical VOC fingerprint not only provides information on the kind of disease present but also on the disease progression. Even the interaction of several pathogens in a polymicrobial environment can be tracked in the exhaled air.

For the experts, breathomics is an interesting diagnostic tool with promising approaches and significant potential. However, a number of obstacles have to be overcome before this potential can be fully leveraged in clinical routine

IT security of POCT devices – not everything is picture-perfect

Until recently, the major challenges surrounding Point-of-Care-testing (POCT) concerned the quality of the results and improving the reagents and the procedures in order to optimise patient care. In the modern clinical environment, however, IT security of POCT devices is becoming increasingly important, in Germany also due to new industry-specific safety standards under the Act on the Federal Office for Information Technology. Professor Dr Thomas Streichert of the Institute of Clinical Chemistry at the University Hospital Cologne, Germany, explains the state of affairs.

At the University Hospital Cologne, about 300 POCT devices are used by approx. 3,000 employees. "Many different users with very different requirements and qualifications," as Professor Streichert describes the situation in a nutshell. Thus, implementing a POCT IT security concept that works smoothly and is feasible in the everyday hustle and bustle of the hospital is no mean feat.

POCT devices and their security gaps

While it makes sense to aim at fully integrating the devices with all data being available in the facility-wide system, this approach does have its pitfalls: the devices being used in the wards might be lying around unlocked and can be accessed by unauthorized persons. This is a major data security gap since the devices contain not only measured values but also personal patient data. In order to protect this data, the devices have to be intelligent, with user identification, access authorisation, role-specific privileges and encrypted communication. For the lab specialist, implementing such a concept strictly across the entire hospital is "an enormous technical and organisational challenge".

High level of security and service

The University Hospital Cologne maintains high security standards. POCT accreditation per ISO 22817 triggered a quantum leap in terms of quality assurance. Every member of the care staff, be it physician or nurse, has to attend an initial training session and refresher training sessions which, in addition, are available online as e-learning modules. Hospital management considered the time and money spent on the training well-invested since compliance with quality standards enjoys top priority throughout the facility. All POCT devices are centrally managed by the hospital's clinical laboratory. This is a sensible approach since the lab medicine specialists have the relevant knowledge and can ensure facility-wide highly competent and target-oriented quality assurance. "The colleagues like to use our service offering. While dealing with the ins and outs of the POCT systems is daily fare for us, the care staff in the wards or the physicians in the ICU are grateful that they don't have to bother. They have important other tasks to tend to." Professor Streichert underlines that this level of service requires a constructive partnership with the IT department: "In the lab, we need quite a bit of IT support, thus, over the years we have developed a very good working relationship with the IT team."

Not always on the same page: data security standards and clinical work

Nevertheless, Professor Streichert identified definite room for improvement: "Despite all the activities, we are not perfect when it comes to IT security." This is partially due to the so-called KRITIS bylaw in Germany which requires the operators of critical infrastructure to establish state-of-the-art protection of their IT systems, components and processes against disruptions in availability, integrity, authenticity and confidentiality in line with Federal Office for Information Security (BSI) specifications. "In order to be able to comply with these requirements, each industry has to develop specific security standards that are reviewed by the BSI for adequacy and suitability." The major hurdle: security standards and everyday operation of a hospital, particularly with regard to POCT, are very difficult to align.

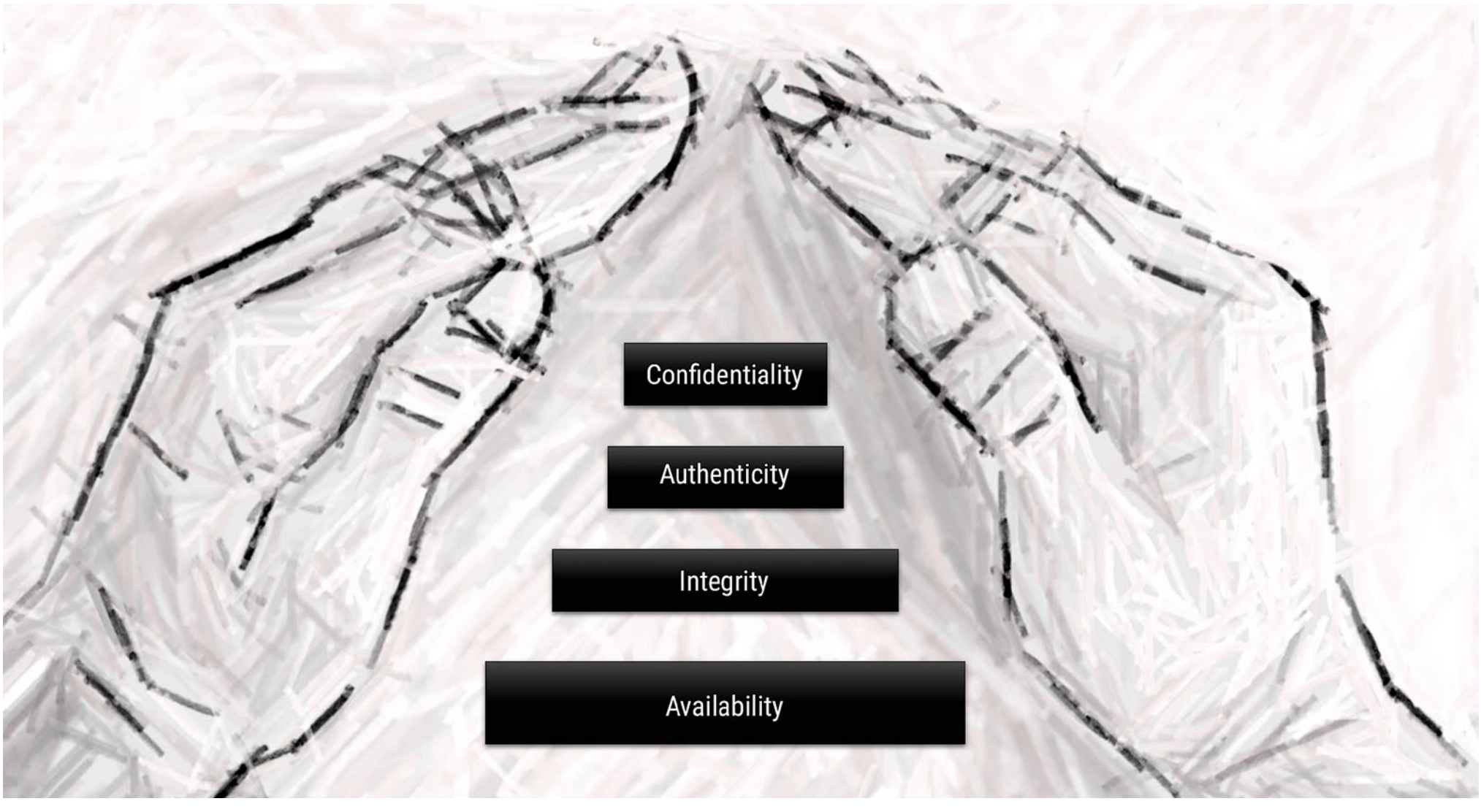
Authentification in a clinical environment

Case in time-consuming point: the blood gas analyser. As a POCT device, it is used in the OR to control ventilation in certain regular intervals. If such a device fails, the consequences for the patient can be fatal. Under BSI law, these devices require a time-consuming and overly complicated authentification procedure. The user name and a 16-digit password have to be entered on a tiny screen – unthinkable in an emergency: much too long-winded and much too error-prone. While technically speaking, the biometric fingerprint might be an option, it requires personal data to be stored on the central servers, which is something that has to be avoided in view of the EU GDPR. "Currently, we scan the employee ID card with a barcode," Professor Streichert explains and adds that theoretically, a second type of authentification, such as a password, is required. This combination, however, is problematic as IDs get lost or end up in coat pockets in the hospital laundry and passwords are forgotten or no longer valid. In the ER or in an understaffed ward, this procedure is unrealistic. Another idea that is being bandied about is a personnel number and a PIN, but this option is currently not technically feasible. There are further potential security gaps such as remote maintenance accesses that are used by external providers, ports, hard disks with unencrypted data or SSDs with data that is unencrypted and/or cannot be deleted.

Round table on IT security

"In view of the complexity of the problem and the fact that we need to establish standards accepted by all stakeholders, we launched a round table with the POCT providers to discuss possible options as well as options that might already be in the pipeline and common denominators." This debate was very constructive – quite surprisingly since today, IT security is a major issue in procurement and there were understandable fears that competing providers were loath to engage in an open discussion. The round table did show that the companies are well aware of all issues and that they are working hard on solutions – and in fact some at least partial solutions seem to be in the wings. One of the major issues that remain to be solved is the user procedure in an emergency context. The good news is that there was a consensus around the round table: technical requirements alone won't do. Any solution has to reflect the everyday situation in a hospital and it has to fit in the overall IT approach. Professor Streichert summarizes the credo: "The leaner the organisation, the simpler the process, the better the solution." A follow-up round table with the same cast of characters is planned for next year.

Professor Dr Thomas Streichert is managing director of the Center for Laboratory Diagnostics (Clinical Chemistry, Microbiology, Virology, Pharmacology, Endocrinology) and acting director of the Institute of Pharmacology, Therapeutic Drug Monitoring at the University Hospital Cologne, Germany. Born in South Africa, Professor Streichert studied medicine in Hamburg, Germany, where he also worked as junior and senior physician. In 2013, the specialist physician for laboratory medicine joined the University Hospital Cologne. He is chairman of the advisory committee "E-learning" at the University Hospital Cologne and member of the German Society for Clinical Chemistry and Laboratory Medicine.



Challenges for laboratory technology

The value of the human microbiome

Report: Sandra Theison

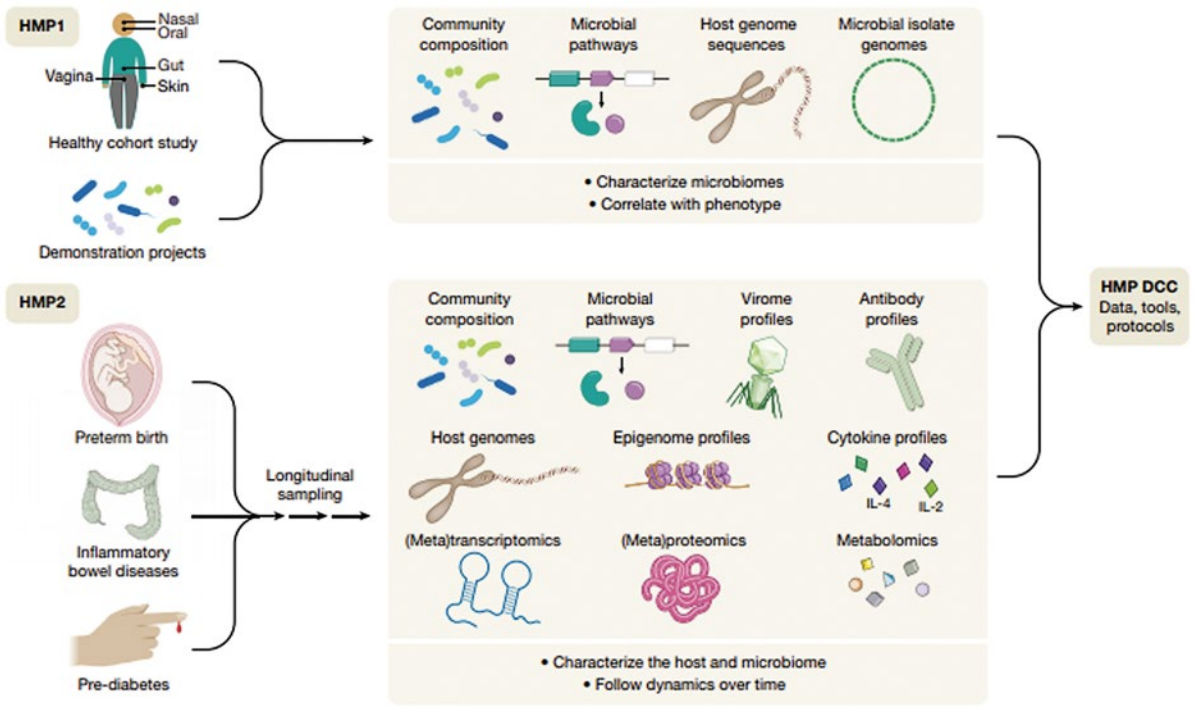
The human species maintains symbiotic relationships with a multitude of microbial organisms that colonise the inside as well as the surface of the body. Scientists, for a long time, underestimated the significance of these organisms for humans. By far the most bacteria of the microbiome can be found in the gastrointestinal tract, particularly in the colon. The number of microbes in the body is estimated to exceed ten times the number of human cells; the body thus contains 100-fold more unique genes than the human genome.

Only 10 to 30 percent of these microbial organisms are culturable. In humans, most bacteria of the gastrointestinal microbiome belong to the four phyla Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria.

In clinical care, the identification of bacteria is crucial to be able to distinguish between bacteria that are colonisers or those that originally cause an infection. Today, this identification is achieved via sequencing of 16S rRNA, particularly if phenotypic methods of bacterial identification are difficult.

The bacterial 16S rRNA gene codes for the subunit 30S of the prokaryotic ribosome 70S and is thus present in the genome of all bacteria. Since it differs from its eukaryotic homologue 18S rRNA, precise identification of bacterial DNA versus human DNA is possible. The gene sequence of this subunit is used in evolution biology as the instrument for phylogenetic analysis.

The 16S rRNA gene consists of approx. 1,500 base pairs and can be separated into several conserved and nine less conserved regions (V1-V9). Since the less conserved regions have little impact on the formation of the subunit 30S, they are hypervariable and specific to particular bacterial species. These regions may thus be used as taxonomic markers. During a polymerase chain reaction (PCR), primers can dock onto the known conserved areas and selectively amplify the variable regions. Sequencing of these DNA sections is usually done by pyrosequencing.



Objectives of Human Microbiome Project phases HMP1 and HMP2

The Human Microbiome Project

The Human Microbiome Project (HMP) is one of the largest biological projects ever. It aims to identify all microbes that colonise the human body and study their roles in health and disease states.

HMP was launched in 2008 by the US National Institute of Health (NIH), focusing on five body sites of a healthy individual: skin, nose, mouth, gut and vagina. In 2013, HMP1 was completed after having collected 14 TB of data from the samples of 300 individuals.

The second phase of HMP, also called Integrative HMP (HMP2/iHMP), was launched in 2014. HMP2 was designed to explore host-microbiome interplay and focused on three topics: pregnancy & pre-term birth, inflammatory bowel diseases (IBD) and onset of Type 2 diabetes (T2D). By way of example, the procedure regarding pre-term birth is described in the figure above shown on this page.

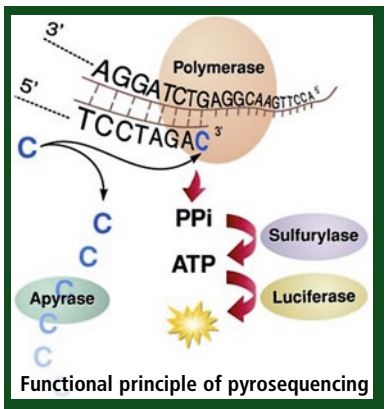
There are significant disparities in the frequency of pre-term birth. In the United States, for example, American women of African ancestry are at a much higher risk of pre-term birth than any other group of women.

16S rRNA analysis was performed and additional profiles from 45 pre-term births and 90 term births were established. Early on in the selection process, it became clear that the percentage of pre-term birth is higher among women of African ancestry.

The analyses showed that women who delivered pre-term exhibited significantly lower vaginal levels of Lactobacillus crispatus and higher levels of 13 other bacterial taxa. Pre-term-birth-associated taxa were correlated with proinflammatory cytokines in vaginal fluid. These findings highlight new opportunities for assessment of the risk of pre-term birth.

The way forward

Future research might focus on identifying and characterising the microbiome with regard to itproteome and metabolome and their interaction with human proteins and metabolites.



Functional principle of pyrosequencing

PYROSEQUENCING

As in Sanger sequencing, the DNA polymerase originating in a primer elongates the complementary DNA strand. When DNA polymerase adds a complementary nucleotide to the DNA strand to be synthesised, pyrophosphate is released. The enzyme ATP sulfurylase converts the pyrophosphate into adenosintriphosphate, which triggers the luciferase reaction where luciferine is turned into oxyluciferine. The intensity of light emission during this process is proportional to the amount of adenosintriphosphate used. Unincorporated nucleotides are degraded by apyrase. Since the individual nucleotides are sequentially added to the reaction, the temporal pattern of light emission allows determination of the DNA sequences.

Improved cap design for blood tubes

Easier blood droplet collection

The MiniCollect Capillary Blood Collection System launched by Greiner Bio-One in 2016, has an improved cap on all its blood collection tubes.

The new version, designed for easier opening, has an increased number of ridges that are also deeper to improve grip and user comfort. The cap rim also overlaps the top of the tube to augment grip and ease opening.

The capillary blood collection tubes offer a gentle way to collect small blood samples for a wide range of analyses, Greiner points out. 'The MiniCollect tube includes an integrated scoop, allowing droplets of blood to be collected easily and hygienically. The wide opening of the tube ensures an efficient blood flow while the increased diameter minimises adhesion to the wall of the tube and facilitates the mixing of the sample.

'The system is perfectly suited for young children, geriatric patients, as well as patients with fragile veins. MiniCollect is also recommended in situations where venous blood collection proves particularly difficult, such as for patients with extensive burns.'

MiniCollect Complete Version

MiniCollect tubes can be threaded into a Premium carrier tube. This combination corresponds to the dimensions of a standard 13 x 75mm tube, the manufacturer adds. With the Complete version, which is already irreversibly assembled with the carrier tube, the advantages – particularly for automated analysis of the sample – are numerous, Greiner reports:

- Changing the settings of analysis instruments is not always necessary since, in many cases, both venous and capillary blood samples can be analysed in the same way.
- MiniCollect Complete tubes generally fit into 13 x 75mm racks, which can be directly inserted into the analyser. The carrier tubes also enable identification with standard label formats.
- MiniCollect tubes are primary tubes. Blood collection and analysis can be carried out in the same tube. It is not absolutely necessary to transfer the sample material into a secondary tube for analysis.
- The cap of the tube can be pierced with an analysis needle while still closed and remains leakproof. It is not necessary to remove the cap, thus ensuring increased hygiene.
- MiniCollect tubes combined with carrier tubes do not need a separate centrifuge. Due to the 13 x 75mm dimensions the tubes can be processed in a standard centrifuge.

Full details: www.gbo.com.

MiniCollect Capillary Blood Collection Tube with newly designed cap.

Combining image-guided diagnosis and robot-assisted treatment

More power in an interventionist's eyes and hands

Siemens Healthineers AG took a big step last October. To incorporate treatment along an entire clinical path, the firm acquired Corindus Vascular Robotics, Inc., to combine image-guided diagnosis with robot-assisted surgery. A couple of months later, the Corindus endovascular robotic system CorPath GRX was used to implant a vascular stent into an obstructed coronary artery – the first use of this minimally invasive procedure to be performed in a German hospital.

Report: Daniela Zimmermann and Sonja Buske

The precision-robot platform is currently the only robot-assisted system for cardiovascular and peripheral, vascular interventions that has FDA clearance and the CE mark. 'We would like to expand our portfolio for therapy,' explained David Winneberger, head of Global Marketing Cardiology at Siemens Healthineers. 'Part of our strategy 2025 is the promotion of image-guided therapy to lower the treatment costs not only for our customers but also the entire healthcare sector.'

The robot is primarily used in cardiology and interventional radiology. The interventions are carried out both by interventional radiologists and vascular surgeons specialising in minimally invasive procedures: 'Up to now we were the interventionalist's eyes,' Winneberger pointed out. 'Because of the new technology we can bring together image- and robot-assisted aspects and now also support the hands.'

Intuitive and fast

In Germany, Professor Holger Nef, Assistant Director of the Cardiology and Angiology department at the University Hospital Giessen, and his team were the first to benefit from the CorPath GRX. They used the Corindus endovascular robot combined with an Artis angiography system from Siemens Healthineers to implant a stent via catheter in a percutaneous coronary intervention. 'I was surprised how intuitive and easy using the robot is, and how fast the procedure can be carried out,' Nef said.

A view from the control centre into the theatre during the first robot-assisted intervention in Germany

Holger Nef taking part in the first robot-assisted intervention in Germany

In a test installation Nef and team have now treated three patients with the help of the CorPath; their objective is to treat 250 patients a year; they aim to establish quality standards for interventional cardiology. Despite the fact that the interventionalists have learnt a lot over the last 40 years, and although the equipment has improved significantly, the treatment of coronary artery stenosis is still susceptible to errors, depending on the various degrees of expertise among those carrying out the treatment. 'The precise placement of the stent or the estimation as to the length of the stenosis very much depend on the experience of whoever is carrying out the treatment,' observed Nef, who plans to carry out a study to illustrate this.

David Winneberger is head of Marketing Interventional Products for Siemens Healthineers. He has experience in both the industry and hospitals as well as in private practice. His comprehensive experience in medical devices, therapy, communication, management, product management and marketing enables him to motivate and lead teams and aim for and reach ambitious goals.

Experienced interventionalists and those with less experience are to work manually as well as with robotic assistance. He expects to see big differences with manual PCI, but not with the robot-assisted procedure.

Doctors as well as patients benefit from CorPath. Because the robot is guided from a room outside the operating theatre, doctors are exposed to much less radiation. 'Up to now, we've had to wear heavy X-ray protection aprons all the time,' Nef explained. 'This is the why literally all interventionalists suffer back problems. Brain tumours in the left hemisphere, as well as cataracts, are further problems observed among doctors carrying out this type of treatment, although the radiation exposure is fairly low, owing to modern equipment. All of this will now be a thing of the past.'

The potential is there

Nef sees further potential in using the robotic systems. Some steps, such as the insertion of wires and catheters, still must be carried out by support staff; however, this is a task which the robot could take over. Winneberger agrees. For him, the planning of interventions and the use of artificial intelligence are two important aspects that should also be researched further.

The question remains as to how exactly the angiography system 'talks' to the robot. How can such different systems be brought together? 'This is actually not that simple,' Winneberger said. 'We have developed a new angiography system with a universal interface, a so-called third-party broker. In the future, angiography will see the use of many different devices and applications from different manufacturers. The third-party broker can connect all of these systems, including the robot, with one another.'

Does the Corindus takeover mean that Siemens will also manufacture robots? The answer is clear: 'In the first instance, the production of robots will remain with Corindus. Everyone has their strengths: Corindus in robot-assisted vascular intervention, Siemens in image-guided intervention, so nobody has to reinvent the wheel. We have established close interfaces between the engineers in both companies to set the course for the future,' the head of Global Marketing for Cardiology explained.

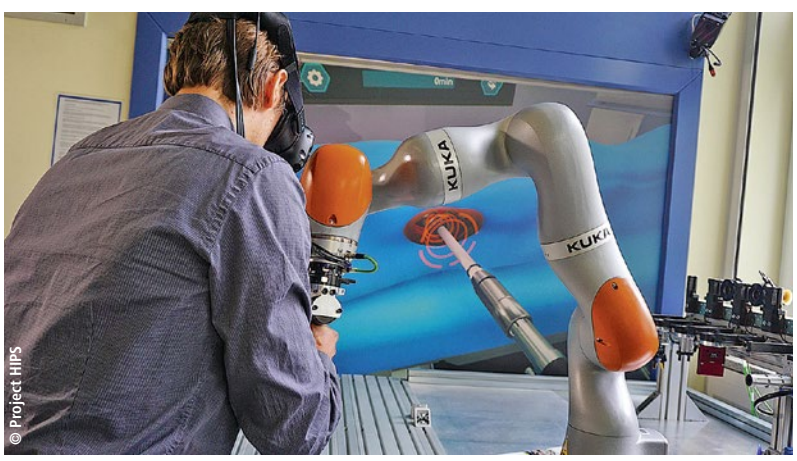
Initially, this future is to see further developments of the existing robot. It is conceivable that it could be controlled from a different hospital: 'The procedure,' Winneberger explained, 'could then take place in a hospital with the doctor who carries out the intervention actually located many miles away,'

Professor Holger Nef MD is Assistant Director of the Cardiology and Angiology department at the University Hospital Giessen. He gained his medical degree in Freiburg and then worked in various roles at the Kerckhoff Clinic in Bad Nauheim, a specialist centre for heart, lung, vascular and rheumatic diseases, as well as transplants and rehabilitation. He is a recipient of the Becht-Research Prize, awarded annually by the German Heart Research Foundation for outstanding research in patient-centred cardiovascular research.

Orthopaedics: Virtual reality training to impro

Simulating acetabulum prepa

More than 200,000 patients undergo hip replacement surgery in Germany each year. To avoid complications and extend the lifespan of the artificial joint, the implants must be fitted precisely in the acetabulum (hip socket). The procedure, particularly milling the acetabulum, is not only difficult but also the technique is difficult to teach and train. This is where HIPS (HüftImplantatPfannenfräsSimulator) – a hip replacement socket milling simulator – comes in.



© Project HIPS

Report: Sascha Keutel

Developed by a research consortium, 'HIPS is the worldwide first virtual reality (VR) training simulator for hip replacement surgery that provides haptic feedback and can simulate interventions that need high and stable forces,' explains Mario Lorenz, from the Technical University of Chemnitz, who initiated this project.

In the future, surgeons in training will practice virtually one of the most complicated steps in hip replacement surgery

The prime goal of the researchers was to improve specialist physician training, as Lorenz underlines: 'Today, specialist physicians in training practice on phantoms, i.e. artificial bones. Material behaviour, however, does not mirror the behaviour of actual bones closely enough which, in fact, also holds true for donor bone material – a rare and extremely valuable resource in medical training and research.'

Specialist physicians in training have to assist in a number of surgical operations before being asked to perform the milling step themselves. 'Wouldn't it be much better if physicians in training had performed several simulations that are as close as possible to the real thing before that crucial moment arrives? Wouldn't it be better to give them an opportunity to develop the necessary feel for the procedure, build self-confidence and allow them to make errors from which they can learn?' Lorenz asks. In minimally invasive surgery, such as keyhole interventions, VR training has been around for about 20 years, Lorenz points out, adding, 'For procedures that need high forces, such simulation products are not available, neither commercially nor for research purposes.'

HIPS users see the virtual patient's hips through VR glasses, while they operate a surgical milling instrument which is connected to a lightweight robot, the BR iiwa. The user has to mill the hip joint's acetabulum – something that is difficult to teach, train and learn. The robot delivers direct haptic feedback by simulating the resistance of a real bone. Thus,

NEW: Fringe Field Navigation (FFN) transforms endovascular surgery

Harmless penetration of tiny vessels

A new technique could enable vascular surgeons to reach even the more difficult body regions. Instead of pushing catheters into minute veins, the system, devised in Canada by Professor Sylvain Martel and team at the Polytechnique Montréal Nanorobotics Laboratory, uses magnetic forces to pull a guidewire, or catheter, into remote physical locations, guiding medical instruments into narrow and complex vascular structures.

The magnetised tip of the device harnesses the fringe field generated by the superconducting magnet of a clinical MRI scanner – coupled with an innovative robotic table – to help overcome one major challenge in endovascular surgery.

As Martel explained: 'For very thin wire – guidewire or catheter – or tethered instruments that must be miniaturised further to navigate deeper through narrow and most often tortuous vessels, or other constrained physiological spaces, the stiffness of the wire is decreasing so much that at some point pushing the instrument is no longer possible.

"If such wire or instrument must be as thin as a hair to navigate deeper through narrow vessels, the only way is to induce a pulling force.'

MRI and robotic table

MRI Fringe field opportunities

'A magnetic field is appropriate,' he continued, 'because it can penetrate the human body without harm and is not affected by various tissue density.

'The most important characteristic for a magnetic field to exert a pulling force on a micromagnet, placed at the tip of the navigated instrument, is the gradient, defined as a change of the magnetic field magnitude over distance.'

The highest magnitude of magnetic field is achieved with a superconducting magnet, such as found in clinical MRI scanner, he said; hence the use of the fringe field of an MRI for this project. Whilst the magnetic field inside the MRI scanner tunnel is uniform, the fringe field outside the machine – which is normally reduced to minimal levels – offered opportunities.

'It's a very-high-amplitude field that decays very rapidly,' he pointed out. 'For us, that fringe field represents an excellent solution that is far superior to the best existing magnetic guidance approaches, and it is in a peripheral space conducive to human-scale interventions.'

Vital: A computerised robotic table

However, the key is a computerised robotic table, he emphasised. This is used to move the patient around the fringe field to induce a high directional pulling force at the tip of the instrument, because the size and weight of the MRI scanner means the machinery cannot be moved to change the direction of the magnetic field.

'So,' added Martel, who directs the NanoRobotics Laboratory at the University of Montréal, 'when the medical specialist navigates the instrument in tortuous vessels, a computer calculates the optimal position for the patient, to exert the highest possible directional pulling force, and then send commands to a robotic table to position the patient accordingly, as the instrument is navigated through a narrow tortuous vessel.'

He believes this is the first time that an MRI fringe field has been used for a medical application.

Movement on all axes

The computerised robotic table, designed by his colleague Arash Azizi, a biomedical engineering PhD candidate, is positioned within the fringe field next to the scanner and can be programmed to move automatically on all axes, to position the patient according to the direction in which the instrument must be guided through their body, using a technique that Professor Martel has dubbed Fringe Field Navigation (FFN). 'We were using the magnetic field inside the MRI scanner to navigate drug carriers for cancer therapy and no-one was using the external field, he said. 'Through that, this fringe field had particularities that no other field has, so we were trying to see if we could use its super high gradient for medical applications. From there, I put together a team to prove that the concept works.'

Standard MRI scanners can be used for the technique – with a robotic table installed in the MRI room – and with no impact on image quality.

The team has spent five years developing the concept and, Martel added, 'So far it's been very successful and showed in pig models that the instrument can go much deeper than when done manually with experts.'

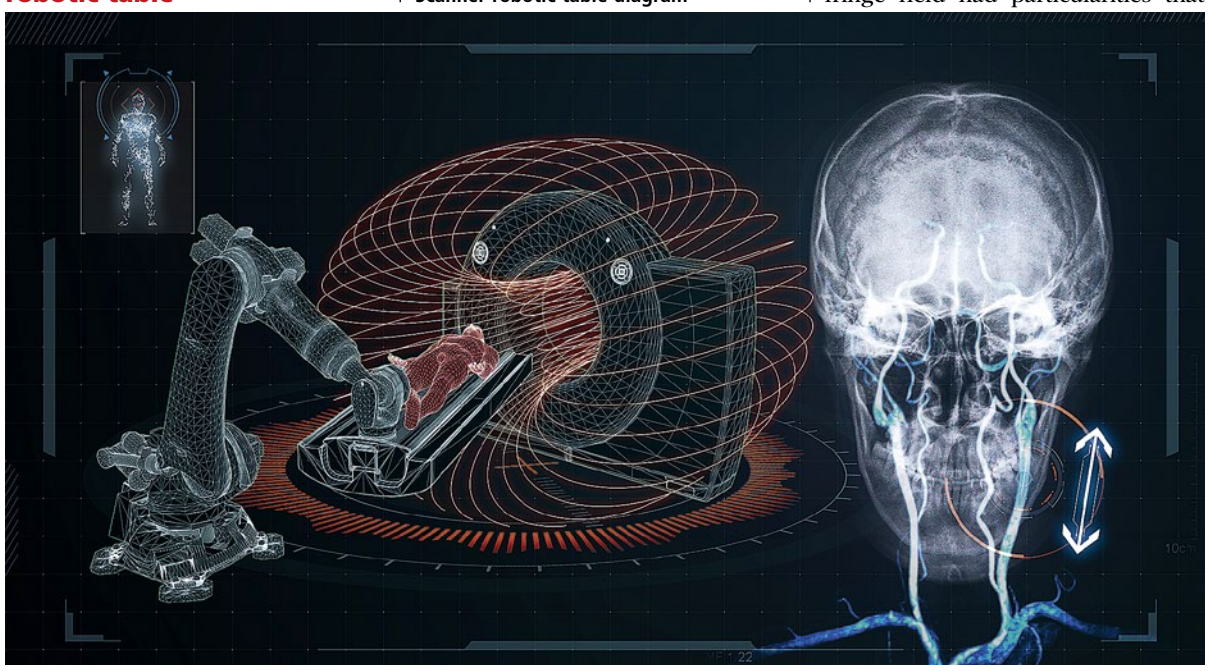
An in-vivo study of Fringe Field Navigation with X-ray mapping has demonstrated the capacity of the system for efficient and minimally invasive steering of extremely small-diameter instruments deep within complex vascular structures which were hitherto inaccessible using known methods.

The robotic solution has promise for diagnosis, imaging and local treatments and could assist surgeons in procedures requiring the least invasive methods, including deep access to the brain for treatment of brain damage such as an aneurysm or a stroke, those needing diagnostics in hard-to-reach vascular regions and in urology.

(mn)

Professor Sylvain Martel is Director of the NanoRobotics Laboratory, Department of Computer and Software Engineering, at the Institute of Biomedical Engineering, École Polytechnique de Montréal, Canada, and a Fellow of the Canadian Academy of Engineering. His main expertise lies in nanorobotics and the development of novel instrumented platforms and related support technologies targeted for biomedical and bioengineering applications. He currently leads a multidisciplinary team involved in research and development of new instrumented platforms for the medical field and in bioengineering.

Scanner robotic table diagram



ve hip replacement

aration

the user acquires a better feel for the forces at work and the area that can be worked.

The simulation is based on real data. To compute the forces and torques when milling the hip, the researchers conducted biomechanical tests with anatomical specimens. 'We found out that we are dealing with up to 200 Newton. Force is needed when the surgeon applies pressure on the acetabulum. The forces applied on the surgeon's wrists when the machine stops is between 20 and 50 Newton depending on the size of the wrist,' Lorenz explains.

With these measurement data, researchers at the University of Bremen, Germany, designed a material model that allows a surgeon to compute, within a millisecond, where the surgical milling instrument meets the acetabulum and what forces are present.

In a next step, a software module was developed that features a user interface integrated by FAKT Software GmbH. The result is an interactive application based on an anatomical model by CAT Production GmbH, which had created the anatomical 3-D models and the virtual operating room (OR).

The team at the Technical University Chemnitz developed the interface with the robot arm to 'tell' the robot the force it has to simulate. 'Originally, the robot was certified for collaborative human-machine tasks on the shop floor. We managed to use the existing interface to provide the user with haptic feedback while maintaining the certification,' Lorenz points out.

Over the next few months, the researchers will conduct a small-scale study to have the system validated by assistant and senior physicians. Subject to approval of funding, the kick-off for the follow-up project will take place in May. The aim is to further develop the system to include more surgical steps. 'We will look at the way the tip of the femoral neck is cut off, the femur is scraped, the shaft is fitted in the femoral neck and the socket is fitted in the milled acetabulum,' says Lorenz.

Virtual milling on the surgical training simulator

© Screenshot Video report of project meeting

The three-year HIPS project received €670,000 from the German Federal Ministry of Economics and Energy (BMWi). The project consortium consisted of the Chair of Machine Tools at the Technical University Chemnitz, the Institute of Computer Graphics and Virtual Reality at the University of Bremen, Leipzig-based FAKT Software GmbH in Leipzig and CAT Production GmbH in Munich.

The medical development partner was the Clinic for Orthopaedics, Trauma und Plastic Surgery at University Hospital Leipzig, ZESBO (Centre for Research on the Musculoskeletal System), the research team Clinical Anatomy at the University of Otago, New Zealand, and the Department of Medical Technology at Fraunhofer Institute for Machine Tools and Forming Technology.

After having completed his informatics program in 2010, at Westsächsische Hochschule Zwickau, Germany, **Mario Lorenz** was appointed assistant at the Chair of Machine Tools at the Technical University Chemnitz in the field of VR and Augmented Reality (AR). In 2016, he also became a guest scientist at the Clinic for Orthopaedics, Trauma and Plastic Surgery at University Hospital Leipzig. His research focuses on the use of VR and AR technologies in production and medical training.

Brain signals control a four-limb robotic system

Tetraplegic moves towards taking walks

Thanks to a four-limb robotic system controlled by brain signals, a patient with a cervical spinal cord injury could walk and control both arms for the first time in a proof of concept. Developed by CEA (French Alternative Energies and Atomic Energy Commission), the system is driven via the long-term implant of a semi-invasive medical device to record brain activity. 'This device is an important step forward in helping people with disabilities become self-sufficient,' said Professor Alim-Louis Benabid, President of the Clinatec Executive Board, a CEA laboratory.

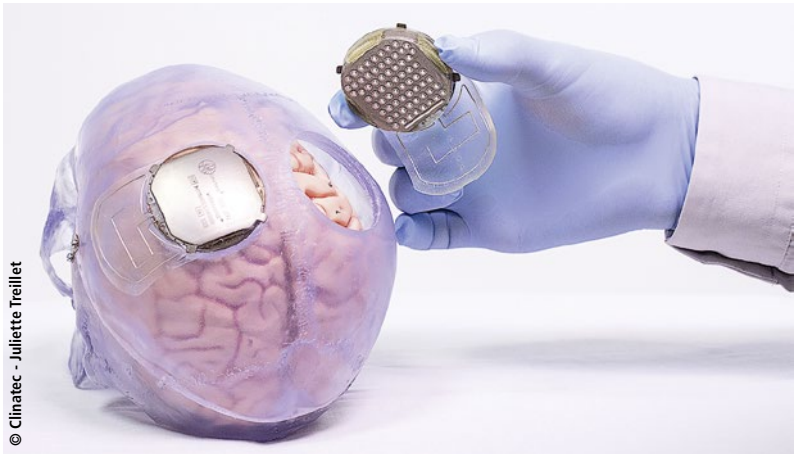
Report: Sascha Keutel

Tetraplegia is caused by a lesion on the spinal cord that prevents the nervous system from controlling all four limbs. To limit dependency and facilitate the mobility of patients with this severe disability, medical doctors, physicians and researchers at Clinatec, a collaboration of the CEA laboratory in Grenoble and Grenoble university hospital, have developed a neuroprosthetic – called WIMAGINE – to decode brain signals and control the exoskeleton. 'Ours is the first semi-invasive wireless brain-computer system designed for long-term use to activate all four limbs,' explained Professor Alim-Louis Benabid. 'Previous brain-computer studies have used more invasive recording devices implanted beneath the outermost membrane of the brain, where they eventually stop working. They have also been connected to wires, limited to creating movement in just one limb, or have focused on restoring movement to patients' own muscles.'

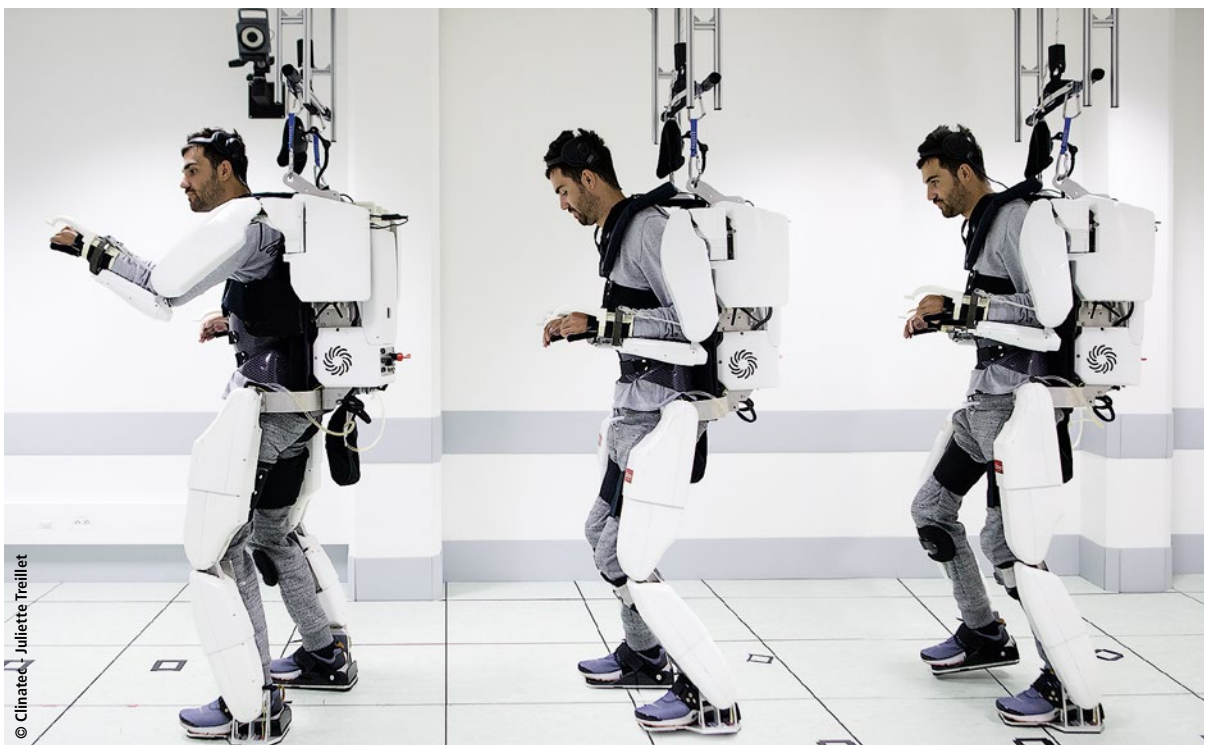
Moving from technology to clinical trials

With the authorisation of regulatory authorities, Clinatec has conducted a clinical trial to test the device on a 28-year-old tetraplegic patient who is paralysed from the shoulders down, with only some movement in his biceps and left wrist.

The neuroprosthetic is the first semi-invasive wireless brain-computer system designed for long term use to activate all four limbs



© Clinatec - Juliette Treillet



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A four-limb robotic system controlled by brain signals helped a tetraplegic man to move his arms and walk using a ceiling-mounted harness for balance

In June 2017, Professor Stephan Chabardes, a neurosurgeon at CHU of Grenoble-Alpes, France, and Medical Director at Clinatec, implanted the devices on the right and left sides of the upper sensorimotor area of the brain, above the patient's dura mater.

The electrocorticograms recorded are decoded in real-time to predict the deliberate movement imagined by the patient and then, for example, to control the corresponding limb of an exoskeleton. 'Innovative adaptive algorithms, based on machine learning, have been developed to decode a large number of degrees of freedom. The exceptional quality of the collected neural signals allowed a stable and robust decoding,' said Dr Tetiana Aksenova, Brain Computer Interface (BCI) signal processing research director from the University of Grenoble, France.

Since the operation, the patient has spent 27 months training the algorithm to understand his thoughts and to progressively increase the number of movements he could make. The patient's progress was measured in terms of how many degrees of freedom he could achieve during tasks, from operating a brain-powered switch to start walking, to reaching out to touch 2-D and 3-D objects. The exoskeleton had 14 joints and 14 degrees of freedom, allowing it to move in 14 different ways. The patient spent 45 days operating the exoskeleton in the lab, and the skills he acquired were reinforced with 95 days spent training at home, with a researcher using an avatar and video game similar to Pong.

A few months after surgery, he was successful 73% of the time during six sessions wearing the exoskeleton. Using the avatar, video game and exoskeleton combined, he covered 145 metres with 480 steps over 39 sessions. When fitted with the suspended exoskeleton, he can take several successive steps and control his two upper limbs in three dimensions. He also can rotate his wrists while sitting or standing. 'Our patient already considers his rapidly increasing prosthetic mobility to be rewarding, but his progress has not changed his clinical status,' Benabid pointed out.

While early results are promising, the researchers note that the system is a long way from clinical application and will require improvements before becoming widely available. Three further tetraplegic patients have been recruited to take part in this clinical trial in the coming years. The next goal of the researchers is to solve the problem of allowing a patient to walk and balance autonomously without using a ceiling suspension system.

'Our findings could move us a step closer to helping tetraplegic patients to drive computers using brain signals alone, perhaps starting with driving wheelchairs using brain activity instead of joysticks and progressing to developing an exoskeleton for increased mobility,' Chabardes concluded.

Radiology in Europe
SPECIAL ISSUE ON LATEST DEVELOPMENTS IN DIAGNOSTIC IMAGING

Gathering around a digital table

Radiology, pathology, medical genetics and laboratory medicine under one roof: many hospitals are toying with the idea of 'integrated diagnostics' but it was the medical management at Geneva's University Hospital that dared to take the first step and consolidate all these diagnostic disciplines in a single organisational unit: The Diagnostic Department.

Report: Daniela Zimmermann and Michael Krassnitzer

'Our longterm vision is a "diagnostic board" within which radiologists, pathologists and geneticists collaborate to create a detailed and structured diagnosis that goes far beyond mere imaging,' underlines Christoph Becker, Emeritus Professor at the University of Geneva and, until 2019, Head of Radiology at the University Hospital Geneva.

In Geneva, joining these disciplines was above all an administrative-organisational procedure, the Swiss radiologist explains. This is not about radiologists doing the pathologists' work, or vice versa, he emphasises: 'We aim to do away with the insular approach of the diagnostic disciplines and arrive at a closer cooperation of the diagnostic specialists.'

Integrate diagnostics – but how?

Becker considers three aspects are crucial for diagnostics integration, first the organisational-administrative aspect. Since this is determined to a large extent by local factors – such as geography; the hospital's organisational structure; distances between departments; budget – no general recommendations can be made.

The second aspect is the digital infrastructure where, as Becker points out, significant differences need to be taken into account: 'Radiology launched the digitisation project 20 years ago and thus is almost fully digitised. In the lab, digitisation has also progressed very well.' Pathology, however, has only recently begun to digitise, one reason being the sheer complexity of the endeavour.

'Whilst today, radiology images are digital from the beginning, a tissue sample is, obviously, analogous. 'The analogous sample and all necessary analytical steps have to be digitised. This requires much more computer power, since colour and high resolution are basic requirements,' Becker points out. In Geneva, the first steps towards digital pathology and a comprehensive digital infrastructure for the entire medical imaging complex are currently being implemented. A central digital archive is planned in which all acquired image data in the University Hospital are stored – radiology images as well as images and videos created in other departments, e.g. dermatology, or images from endoscopies.


Source: Nephron (Wikimedia Commons; CC-BY-SA 3.0), Mashup by HiFi-Ehrenfeld

Successful workflow

The third crucial aspect of integrated diagnostics is a workflow that allows to identify and remove discrepancies in diagnostic procedures: today it may well happen in complex clinical situations that different diagnostic disciplines arrive at different conclusions in their assessment of findings. This should be avoided by intelligent diagnostic processes aiming at a synthesis of the diagnostic findings: Diagnostic specialists and their tools must be able to communicate more directly about discrepancies in their assessment.

A first small step was made several years ago at the University Hospital of Geneva. 'During an image guided biopsy in the radiology department, a pathologist is present and has access to the necessary technical infrastructure for staining and microscopic evaluation in order to assess the sample right away for its quality. If the sample is insufficient, or cannot be used for whatever reason, a second sample is taken immediately.

'The pathologists like being on site because they appreciate the direct communication with colleagues. The patients also benefit because they don't have to come back for a second biopsy,' Becker explains.

Today, treatment strategies for individual patients are often decided jointly in multidisciplinary meetings including all necessary clinical specialists. Typical examples are the tumour boards in oncology. 'These tumour boards are time-consuming and difficult to organise,' the radiologist points out, 'because to get the different specialists to meet at a certain time, at a certain place, is not easy. A specialist's time is very valuable, and the time spent to align the different complex diagnostic findings during the tumour board meeting reduces the number of patients who can benefit from common decisions,' Becker underlines.

Therefore, discrepancies between the findings of the individual diagnostic disciplines should be identified early on and resolved before the tumour board convenes. 'Ideally, radiologists, pathologists and other diagnostic specialists should provide a consensual integrated diagnostic report, which is then the input for the tumour board,' Becker explains. 'While this might not be necessary in all cases, he adds, 'it will be very useful in many special and complex cases, with a clear benefit to both treating physicians and patients'.

Radiologists and pathologists should learn to communicate

Communication: this is easier said than done because, in a way, radiologists and pathologists speak different languages. While radiologists and macroscopic pathologists both assess morphology, they look at the issue at hand from very different vantage points. Radiology strives to offer an overview of body regions or organs; pathology in turn offers insights that are anatomically less comprehensive but – with the help of a microscope – go deeper to the cell and immunology level. Evaluating the results of each of these methods in a separate or 'insular' way can be misleading, due to the heterogeneity of tumours. For a best possible diagnostic workup it is therefore imperative to look at the complementary data in a joint context. 'Having said that, we must also point out that modern technology increasingly enables radiologists to look at deeper-lying features of tissue structures,' Becker concedes, adding that functional imaging has now become routine. For instance, CT perfusion shows how fast tissue takes up blood; diffusion-weighted MRI offers insights into the cellular level of the tissues, and positron-emissions tomography (PET) provides information on metabolic activities, such as glucose consumption. 'MRI parameters, such as T1 or T2, enable us to interrogate tissue with different non-invasive parameters,' Becker points out, adding that all data 'need to be merged to be able to understand a patient's exact status'.

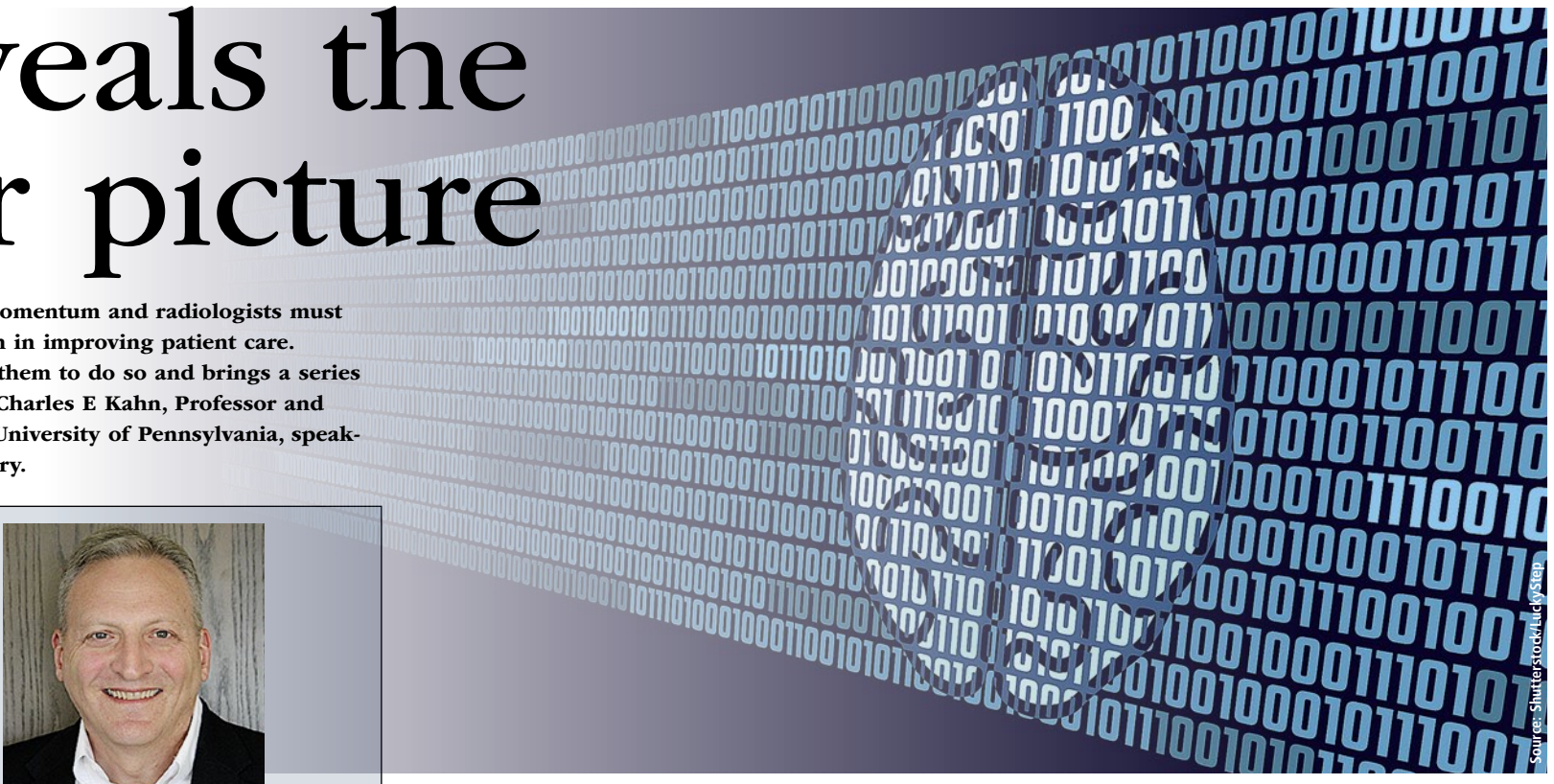
Patient empowerment

Speaking of the patient, Becker is deeply convinced that, in the future, patients will be increasingly involved in decision-making. 'Patients of the younger generations want to know what's going on. Some want to be present when their case is discussed and when further steps are decided. They want to hear arguments; ask questions. In Geneva, even today some patients take part in the tumour board meeting on their case.' This concept of 'patient empowerment' can be summarised with the modern slogan 'nothing about me without me'. Studies have shown that patients, above all younger ones and women, with online access to their electronic patient records, call up their radiology findings more often than any other clinical documents.

However, patient empowerment also raises questions: when findings become ever more detailed and complex, when parameters are included that only specialists can decode, how can patients understand the findings? 'Enter artificial intelligence,' Becker suggests, with a smile. Why not have algorithms translate the highly complex findings in layperson's terms, he asks. This seems the only viable solution because, as he points out, 'manually translating these findings and integrating them in routine clinical workflow is so time-consuming that it can be done only with the help of computers.'

Professor Christoph D Becker gained his medical doctorate and specialist radiology training at Berne University, Switzerland, followed by a two-year clinical fellowship in interventional radiology at the University of British Columbia, Vancouver, Canada. He returned to Berne University Hospital as a staff radiologist and also acquired his university teaching licence. In 1994, he joined Geneva University Hospital to become head of Interventional and abdominal radiology. In 2001, he was appointed as tenured professor and Vice Director of the hospital's radiology clinic, followed by an appointment as Director in 2004. As a full professor he also chaired the clinical department of medical Imaging and the academic department of radiology and medical informatics of the faculty of medicine. He was involved in setting up the new clinical diagnostics department. In 2019, following the end of his tenure as professor and director of the clinical and university departments he became an Emeritus Professor at the University of Geneva.

AI reveals the bigger picture


Source: Shutterstock/LuckyStep

Value-based healthcare is gaining momentum and radiologists must increasingly show their contribution in improving patient care. Artificial intelligence (AI) can help them to do so and brings a series of new opportunities, according to Charles E Kahn, Professor and Vice Chairman of Radiology at the University of Pennsylvania, speaking at a meeting in Madrid in January.

Report: Mélisande Rouger

AI can do a lot to improve radiology's role in healthcare, from choosing the right procedure to predicting diseases, Kahn told delegates at Triángulo, a meeting organised by prominent Spanish radiologists including Luis Donoso Bach (Barcelona), Luis Martí-Bonmatí (Valencia) and Eduardo Fraile Moreno (Madrid).

Charles E Kahn is Professor and Vice Chairman of Radiology at the University of Pennsylvania. He is also the Editor of Radiology: Artificial Intelligence, an official journal of the Radiological Society of North America (RSNA).

Improving procedure selection and findings

First, AI can improve procedure selection, a process in which radiologists are not often involved, although 'that may be the most important part of the job in radiology,' Kahn pointed out.

Deep learning (DL) systems, for example, could extract information from electronic health records to look at patterns of previous patients with previous diseases, to know which procedures worked best for them. Based on that information, algorithms could be created that will help select imaging procedures more precisely.

For protocol selection with contrast examinations, DL could help chose how contrast should be administered – intravenously or orally – and determine scan parameters, to better answer clinical questions.

The way radiologists view studies in their PACS is not optimal right now and AI could help improve image display based on previous preferences, Kahn suggested. 'DL could help automatically to arrange image display by using previous patterns and identify image series that are likely to be useful. Some PACS vendors are developing intelligent ways of mapping images that watch what you do when you select the images,' he said.

DL algorithms can also help reconstruct MRI images from k-space data and provide an alternative to iterative reconstruction for CT, to further reduce radiation dose.

Many efforts have been put into improving findings to advance image segmentation to determine the extent of disease; assess diagnosis, staging and imaging phenotypes; and monitor disease.

AI segmentation tools could alleviate the radiologists' workload and improve their performance, by tracking and measuring lesions to adjust therapies in follow-up CT scans in cancer patients.

Systems using deep convolutional neural networks have been developed for automated real-time triaging of adult chest radiographs on the basis of the urgency of imaging appearances.

Such systems have notably helped sort out patients in chest radiograph triage in the UK, reducing average reporting delay from 11.2 to 2.7 days for critical imaging findings, a study published last year in Radiology showed (Annarumma et al. Radiology 2019; 291:196-202).

Matching results with pathology and following up recommendations

Hospital electronic systems contain large amounts of written information, which can be extracted and fed to AI systems for training purposes.

Combining machine learning (ML) and natural language processing (NLP) to categorise tumour response in radiology reports can be an interesting solution. At Penn Medicine, those reports all feature a code that indicates tumour growth or regression, to enable to extract information that is relevant for patient management.

Matching radiology data with pathology information can be key to show value of imaging studies in the healthcare continuum. 'An ideal system would link pathology results with radiology procedures so that radiologists could be sure to know the outcomes of their biopsies,' Kahn said.

AI reveals the bigger picture and enables things to be done at a scale not possible before, he added.

Predicting disease is part of that wider scheme. One way to predict disease is by taking measurements with DL during opportunistic screening, a strategy that is gaining momentum.

'Opportunistic screening uses AI tools to search images routinely for conditions that suggest a health risk. For example, AI can measure coronary artery calcification on chest CTs to assess a patient's risk of heart disease,' he said. 'Having the information that early means being able to provide better patient prognosis.'

Opportunistic screening with AI may also prove useful in other conditions, such as osteoporosis, abdominal aortic aneurysm, atherosclerosis, emphysema and cirrhosis.

The Centre for Practice Transformation (CPX) in Penn Medicine's Radiology Department unites efforts in patient management, IT, and quality improvement initiatives and innovation. Some of their projects include the implementation of an imaging clinical decision support; fit-for-purpose exams; patient-oriented reports; radiology-pathology integration. On the disease front, the Centre is tackling lung cancer screening and nodule tracking; multiple sclerosis plaque analysis; abdominal organ volumetry and fat analysis.

The centre also promotes report text analysis using NLP for recommendation tracking.

'We know that a large proportion of our recommendations are never acted on. We want to ensure that patients are getting the care they need,' Kahn concluded.

Harnessing the benefits

Blockchain to enhance care

Blockchain is a concept that could have significant benefits for healthcare – particularly in radiology – but several challenges remain. Although an effective conduit through which to share data and medical images, particularly across health systems, one drawback is speed, given the amount of data that can be involved.


Source: Shutterstock/Sashkin

Report: Mark Nicholls

However, Professor Morgan McBee, paediatric radiologist and imaging informaticist, believes blockchain advantages mean harnessing its potential within a medical context is worthwhile.

A blockchain is a growing list of records linked by using cryptography, and as a distributed ledger, can record transactions between two parties efficiently and in a verifiable and permanent way. 'As blockchain is an immutable distributed ledger technology, the most obvious application in healthcare is medical records, including medical imaging data,' McBee explained.

The lack of a single-payer healthcare system in the USA, for example, means that individual healthcare systems and hospitals control their own electronic medical records – with little data sharing. McBee described the following scenario: a cancer patient living in Minnesota for six months, and Florida for the next six, has two healthcare systems that can view each other's medical records and radiology reports, yet radiologists and other healthcare providers cannot see images performed at the other system. Whenever she has a scan at one hospital, this patient must either have them burn a disc and then transport it herself, or mail it, or have the images sent electronically so that two different healthcare systems have access to the other's imaging data. 'If she could store the images in a distributed ledger, such as blockchain, or control access to the images stored in a cloud environment via a distributed ledger, she could grant access for one healthcare system to imaging performed at the other, thus obviating the need for her to manually carry discs or manually push images electronically.'

This scenario is not confined to the USA, he pointed out. The ability to share medical imaging data across Europe can enable more robust research, artificial intelligence, and the ability for patients to control their own medical records to bolster compliance with the General Data Protection Regulation (GDPR).

'Specific to medical imaging,' he added, 'blockchain can be used for image sharing to include patient-ownership of their own images, tracking of medical devices, research, teleradiology and artificial intelligence.'

Professor Morgan McBee is a paediatric radiologist and imaging informaticist, as well as Assistant Professor of Radiology at the Medical University of South Carolina. He has leveraged his keen interest in IT throughout his radiology career to improve systems and patient care.

Other more general use examples in healthcare include medical records, other supply chain management, billing, and credential verification.

A blockchain implementation that enabled patient-ownership of medi-

Continued on page 20

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Cut through the AI hype

An Enterprise Imaging (EI) strategy addresses and solves problems before AI is adopted

Report: Mark Nicholls

It's time to cut through the hype surrounding artificial intelligence and begin to understand the reality in terms of application in radiology.

With many different algorithms available that cover a growing array of diagnostic and interpretational areas, Dr Anjum Ahmed believes hospitals and care providers now need to ask the right questions when weighing up AI implementation in their clinical practice.

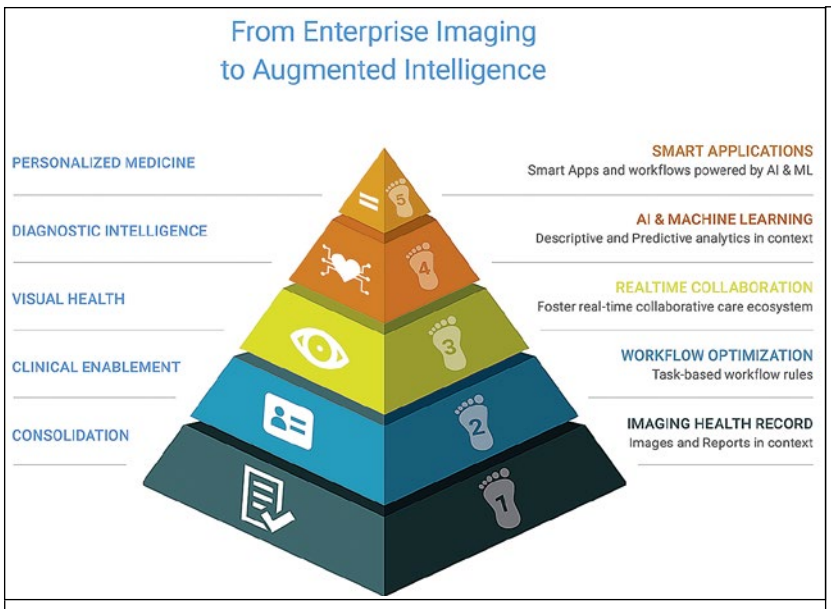
Not only is choosing the right application(s) imperative – and particularly asking key questions about what clinical programme they want to improve and the clinical challenges they want to address – but they must also focus on effectively embedding it into their workflows, instead of deploying AI on its own.

In recent months, Ahmed, who is Chief Medical Officer for Agfa HealthCare, highlights this scenario in his presentation 'Practical AI in Radiology: Ensuring value-based application and improving outcomes', delivered at international radiology congresses.

Stressing the need to 'cut through all the hype about AI' and to understand industry dynamics, he pointed out that, with the array of algorithms now available, it is challenging for healthcare providers to decide where to begin. 'The discussion has initially been whether AI is going to replace physicians,' he added, 'but I think the realisation now is that AI is not there to replace physicians; it is more about how to validate and use AI in clinical practice with measurable benefits.'

In terms of industry dynamics, he said, the issue for care providers is knowing which imaging-use cases and applications are useful for their clinical needs, the regulatory clearance status, and which are still in the R&D phase. 'There may be a dozen algorithms on the market already for the same clinical use case, so the question is how to decide, as a care provider, what direction to go in,' he said.

That becomes further complicated, for example, with AI Apps focused on detection of cancers, as each of the AI apps may be focusing on a specific feature or functions. For example, one AI vendor might be offering a Chest CT nodule detection algorithm, while another vendor may be focusing on nodule analysis and automated measurements. How do we then embed these multiple AI algorithms into workflows while keeping in mind that, internationally, there are variations in terms of how care teams are organised and review clinical findings.



When creating a clinical programme-focused approach, Ahmed believes that embedding AI into existing workflow offers a strategic opportunity in radiology.

This has brought into focus the importance of an Enterprise Imaging (EI) strategy that addresses and solves some of the basic fundamental problems before you even bring AI into the mix, Ahmed pointed out. 'The core of this strategy is establishing a data rich imaging repository…and on top of that data lake, having a workflow layer that can read into the metadata that AI algorithms will generate; that is where a seamless user experience demanded by radiologists and clinicians is embedded into their workflow, providing real-time analytical intelligence.'

He pointed to Agfa's Enterprise Imaging rules-based workflow engine that organises, sorts, prioritises and drives tasks, and is customisable for a specific organisation's needs.

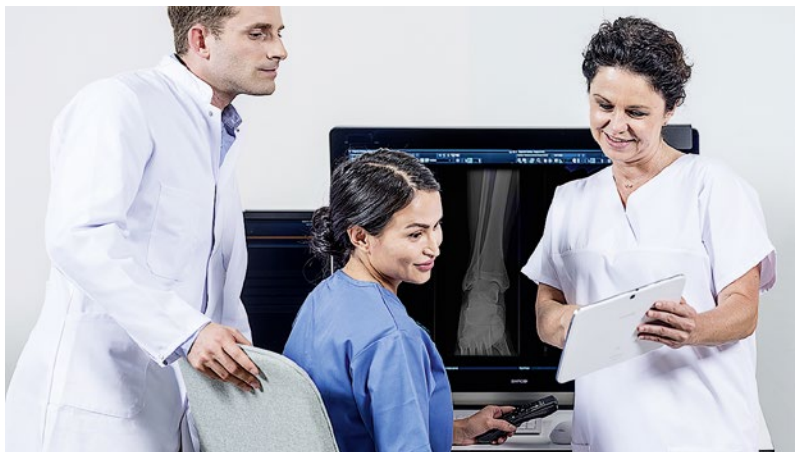
'The rules engine has multiple criteria that can be used to automate some of the routine tasks that diagnosticians or radiologists are manually conducting today, even populating automated structured reports' he said.

He highlighted that some early adopters who have implemented AI algorithms in isolation of their PACS, realised that their radiologists were not as productive as before, because AI was not embedded into their workflow. 'This is where Agfa comes in with a strategy around embedding those best-of-breed AI applications into the workflow focusing on clinical programs,' Ahmed said.

'Start-ups that have developed AI algorithms have done a good job in developing niche applications, our strength is the purpose-built Enterprise Imaging platform ecosystem, and how we take a modular approach embedding these best-of-breed AI applications and ensure that the radiologist has a seamless experience for the selected use case.'

Agfa believes that a governance team of interdisciplinary clinical leads sits at the heart of an effective EI strategy. The EI solution should enable workflow orchestration and real-time tools for communication and interdisciplinary collaboration.

A Chest X-ray done on a patient in ICU might indicate tube malposition or pneumothorax, or another critical finding picked by AI; The rules-based workflow engine should then be able to escalate X-rays with critical findings at the top of the radiology worklist, prioritise the review task and generate a preliminary report for the diagnostician to review.



Anjum Ahmed MBBS, MBA, is Chief Medical Officer and Global Director for Imaging IT Solutions (steering strategic innovation initiatives for Enterprise Imaging) at Agfa HealthCare, which he joined five years ago after 12 years at a top-tier global healthcare vendor, he was responsible for launching Agfa's innovation strategy relating to AI and other 'ologies' (beyond radiology/cardiology).

Another point Ahmed made was about value-based care alignment (cost, quality, outcomes) and the impact on outcomes (clinical, operational, financial) and an evidence-based approach.

'An algorithm may be very good with its sensitivity/specificity results based on retrospective analysis of data during development, but what does it mean in terms of clinical productivity, early disease detection and improved outcomes based on prospective studies?' he asked.

The 'holy grail' is about bringing care program-focused best-of-breed applications to enable precision diagnostics.

'It's about educating the audience; while the hype around AI is subsiding and reality is now upon users, the sense of realisation is that they should not be creating technology silos associated with these multiple AI algorithms, Ahmed concluded. 'That's where the user community and care providers are beginning to realise that a platform strategy with EI makes sense because it builds a secure, modular and scalable ecosystem.

'It's not just the workflow, but more about the role diagnostic imaging can play with the use of AI, becoming powerhouses of evidence-based analytical intelligence, helping to improve care outcomes on the path towards precision health.'

Blockchain to enhance care

Continued from page 18

cal images could be used directly by a patient, and anyone they grant access to, such as family members or healthcare providers. 'A blockchain implementation for credentialing could be used by hospital administrators to have faster and trustworthy verification of physicians' credentials,' he added.

'It is immutable and therefore data can only be added and not removed. Once added, data cannot be changed,' McBee emphasised. 'This is not to say that a medical record stored on a blockchain is static, but it means that you have a perfect record of every single thing that has been added all the way back to when the record was initially created, in a concept known as data provenance.'

Challenges remain, he said, but when viewed as a distributed ledger technology, blockchain can be a powerful tool. However, while one of blockchain's strongest benefits is security, 'it is also one of its biggest pitfalls.' If a blockchain implementation is public (permission-less), the data is available for anyone on the network to view it, and while still secure and encrypted, any future vulnerabilities in the underlying encryption scheme could reveal sensitive medical information.

This risk can be mitigated through the use of private (permissioned) blockchains where only certain actors (hospitals, healthcare providers and patients) have access to the data.

Another challenge is speed, with blockchain being orders of magnitude slower than a traditional database, when dealing with large volumes of data and millions of patients. McBee also indicated that, with current blockchain technolo-

Artificial Intelligence

onising medical and analysis with AI

At Fujifilm's booth at the European Congress of Radiology 2020 (ECR), it will be possible to see live demonstrations of AI delivering enhanced workflows. Fujifilm will also demonstrate how AI will be utilised in the future through the review of multiple cases in the same Synapse PACS technology that radiologists use today.

At the booth it will be possible to see the FDR nano with AI CAD software Lunit insight CXR which provides abnormality score by heatmap for 10 main chest abnormalities. In a hospital, a typical emergency room is crowded with equipment and staff. The extremely lightweight FDR nano delivers freedom of movement with its four-wheel caster and provides an advanced workflow and improved patient care pathway.

Fujifilm announced that it will preview its new FDR D-EVO III DR detector, the world's lightest flat panel detector. The innovative design of this device is a world first, because it removes the traditional glass substrate from the capture layer, which allows a much lighter weight compared to previous models, improving durability, while still maintaining Fujifilm's renowned image quality at a low dose. The next generation 14x17" detector retains all of the ground-breaking features of the FDR D-EVO II including its sleek design with smooth, tapered edges for easier positioning, antibacterial coating, memory mode and is compatible with the same accessories. Thanks to the lighter weight, enhanced durability and streamlined design, this new detector will be ideal for demanding high-volume portable environments.

Women's health

In the breast imaging segment, Fujifilm›s strong commitment to continuous technology evolution and a clear commitment in providing innovative solutions in women's health products has led to the release of the AMULET Innovality Full Field Digital Mammography system. With its state-of-the-art features in dose reduction, image quality and advanced clinical applications, Amulet Innovality represents Fujifilm's capability to convert pure technology insights into drastic care improvements. At ECR it will be possible see live demonstrations of the Amulet Innovality. This device utilises Fujifilm's unique a-Se direct conversion flat panel detector with hexagonal pixels to produce clear images with a low X-ray dose. This system makes use of an intelligent AEC (i-AEC) combined with advanced image analysis technologies to automatically optimise the X-ray dosage for each breast type. The Amulet uses dynamic image processing DV2m enhancing breast composition analysis, for optimised visualisation of structures. Moreover, thanks to advanced proprietary technologies such as ISR and FSC, Amulet Innovality is capable of a significant reduction in the dose to the patient per view. 'S-View' synthetic 2-D processing is also capable of reducing the number of exposures in the event of a screening examination performed with tomosynthesis technique (vertical and lateral approach)

gies, storage of actual imaging data in a blockchain is unlikely.

'Some of the concerns surrounding AI algorithms are that a 'black box' could be alleviated by blockchain. All data that algorithms are trained on can be tracked and verified, as can all outputs of the algorithms,' he said.

'Blockchain is definitely a viable solution for certain use cases, but it is far from a panacea and cannot solve all of our problems in healthcare,' McBee concluded. 'I think the biggest impact of blockchain on healthcare can be data sharing.'

Mistakes in breast imaging also harm radiologists

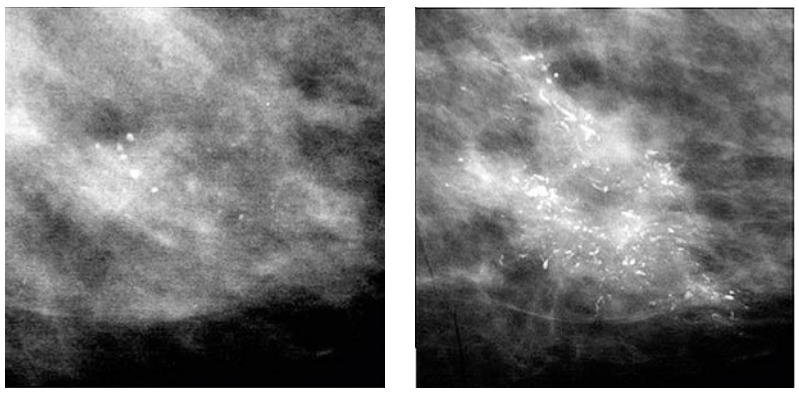
‘Error is inevitable – we are human’

Report: Mark Nicholls

Errors in breast imaging: the subject is vexing. How to avoid or address errors are also concerning. These subjects lay at the core of a presentation to radiologists during the recent annual congress of the British Institute of Radiology, when consultant radiologist Dr Rosalind Given-Wilson described the how, where, and what of errors or near misses, along with their impact on patients and radiologists. She also outlined potential remedies and lessons to be learned.

Errors, she noted, are inevitable – in the USA, for example, up to 100,000 patients die annually due to safety incidents; in the UK’s NHS adverse events occur during 10.8% of hospital admissions, and a third result in death or severe morbidity; in radiology, 2-20% of imaging reports show clinically significant errors.

Dr Given-Wilson, a breast imaging specialist at St George’s University Hospitals NHS Foundation Trust in London, pointed out that in the individual, errors can be about failure to perceive, interpret or adequately assess investigations or biopsy, and failure to communicate.



Breast image where calcification was interpreted as benign but later (as seen in a second image) proved not to be the case

Types of radiological errors include missed discovery (42%); failure to continue to search after finding the first abnormality (22%); abnormality attributed to the wrong cause (9%); lesions being outside the area of interest on the image (7%); over-reliance on a previous radiology report (6%); failure to look at old films (5%); inaccurate or incomplete clinical history (2%); and poor technical examination (2%).

Error examples

Given-Wilson also gave specific examples of errors, such as a swallowed coin in the oesophagus missed by radiologists who were looking for something else; calcification interpreted as benign, and a breast cyst identified but cancer missed.

She then referred to a 42-year-old female patient, with PET/CT undertaken for staging for oral cancer in June 2017. The report identified possible further primary cancers in breast and kidney and, whilst referrals were made by letter to renal and breast teams, further investigation was undertaken of the kidney, but not the breast. In September 2018, the patient presented to clinic via her GP with node positive locally advanced breast cancer at the site previously identified on PET/CT.

Unclear reporting

‘We can either fail to see, or fail to interpret,’ she said, ‘but there are also errors involving communication where imaging may have been abnormal but not acted upon, the report not being clear or not getting to the right place.’ In dealing with errors, there is the need to recognise, investigate and to learn from them, Given-Wilson advises. ‘It’s important to investigate with a root cause analysis, to identify the contributing factors that led to adverse events to decrease the likelihood of future occurrence.’

Rather than looking for individual blame, focus should be more on systems’ failures, she added. Radiologists can be affected by errors and suffer stress or burnout. This can be off-set with relevant support from colleagues, family and friends, legal protection societies, occupational health and counselling and training in preparation for difficult conversations.

In an era of increased complexity of modern medicine, improved teamwork is also of value in helping to avoid errors and near misses.

Effective communication needs structured reports, clear classification and advice regarding the next steps, and a further question is whether, as part of the communication process, a report should be sent to the patient, as is mandatory in the USA. ‘Do we empower the patient?’ Given-Wilson answered her own question: ‘I am not sure that we do.’

There is also a need to temper public expectations. ‘Radiology and radiologists are not perfect and, even if we have AI, it’s still not going to be perfect,’ she said. ‘Error is inevitable – we are human – but it is damaging to radiologists, as well as patients.

We need to look for it and benefit from it by learning and we really need to consider how we convey the imperfections of screening and diagnostic radiology to the public.’

Dr Rosalind Given-Wilson is a consultant radiologist at St George’s University Hospital NHS Foundation Trust in London, of which she was medical director until 2015. A breast imaging specialist, who has been pivotal in establishing screening programmes, her research interests include breast imaging optimisation.

Wireless lesion localisation

Technology gets breast cancer patients ‘off the hook’

Breast conserving surgery demonstrates the need for Innovation to drive solutions in healthcare, says Dr Wolfram Malter, Senior Consultant and head of the Breast Centre, at the Obstetrics and Gynaecology department, University of Cologne.

“In any given patient’s continuum of care, there are two main parts to his or her journey: before and after a diagnosis. For the latter, treatment is of course required. While treatment options are certain to vary depending on the diagnosis, there are a few challenges that remain consistent in today’s healthcare landscape. In addition to providing accurate and high quality clinical care, clinicians also need to consider other external pressures, such as maintaining both an overall positive patient experience while managing a heavy work schedule. Additionally, clinicians often must take into account how their approach to care will affect not only their patients, but any subsequent clinicians who might need to work with the patients in the next phase of their journey of care.

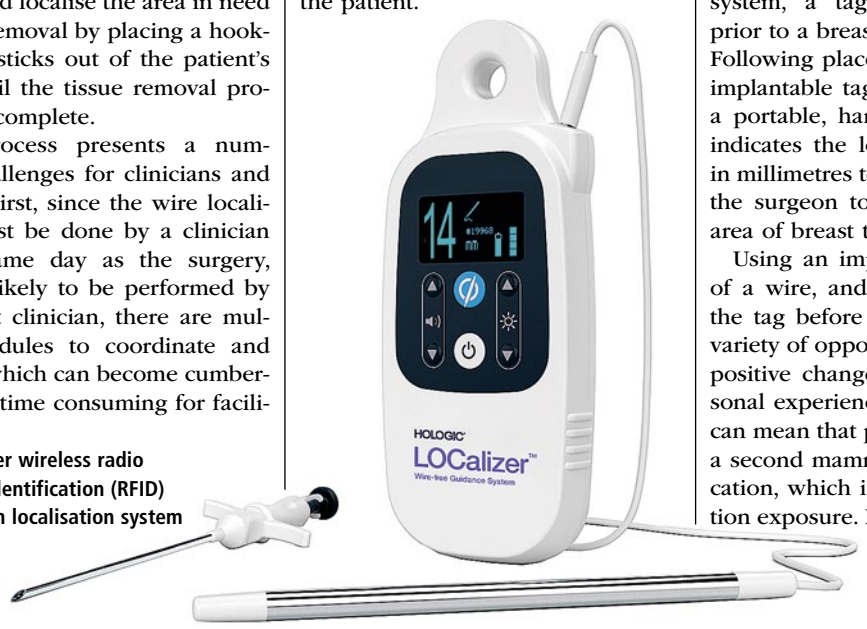
A viable alternative to mastectomy

One way to illustrate this point is by examining a breast cancer patient’s experience with breast-conserving surgery – a viable option and alternative to mastectomy for patients whose cancer is detected early enough – as is the case in most patients in Germany.

Traditionally, when women have breast-conserving surgery after a cancer diagnosis, either radiologists or surgeons – depending on the facility – place a titanium clip using ultrasound or mammography to mark the breast lesion, whenever they cannot be detected otherwise. Then, on the same day as the surgery the clinician must image the patient for a second time to locate the clip and localise the area in need of tissue removal by placing a hookwire that sticks out of the patient’s breast until the tissue removal procedure is complete.

This process presents a number of challenges for clinicians and patients. First, since the wire localisation must be done by a clinician on the same day as the surgery, which is likely to be performed by a different clinician, there are multiple schedules to coordinate and manage, which can become cumbersome and time consuming for facilities. Additionally, when placing the hookwire, radiologists can potentially miss the clip target altogether, or the wire could even dislocate during the time it takes from the patient to move from the imaging room to the operating room. As a result, the surgeon may not be able to locate the lesion and excise the tissue.

In addition, there is a need for a second mammogram to place the hookwire, as ultrasound cannot locate a previously placed clip reliably. This increases the amount of radiation patients receive, while the protruding wire can also add additional discomfort to an already emotionally heightened situation for the patient.



The LOCalizer wireless radio frequency identification (RFID) breast lesion localisation system

As there is clearly room for improvement in the standard wire localisation process for breast-conserving surgery, it is up to clinicians and healthcare professionals to seek out solutions that exist to address these issues. For example, at the Breast Cancer Centre of the Department of Obstetrics and Gynaecology, at the University Hospital of Cologne, Germany, I have had the opportunity to use a new technology that can help mitigate some of the key issues clinicians face today during breast-conserving surgery.

With the LOCalizer wireless radio frequency identification (RFID) breast lesion localisation system, a tag can be implanted prior to a breast-conserving surgery. Following placement, this miniature implantable tag can be detected by a portable, handheld reader which indicates the location and distance in millimetres to the lesion, enabling the surgeon to identify the correct area of breast tissue for removal.

Using an implantable tag instead of a wire, and being able to place the tag before surgery, opens up a variety of opportunities for potential positive change. Based on my personal experiences, this new process can mean that patients will not need a second mammogram for clip relocation, which in turn reduces radiation exposure. I have also found that the ultrasound visibility of the RFID chip is better than a standard clip. Finally, I would imagine that any patient would be happy to avoid a situation in which she would have to endure a wire protruding from her breast, which is certainly both physically and emotionally uncomfortable.

This technology is just one example of how clinicians and healthcare professionals can turn to innovation to combat the inefficiencies and shortcomings of conventional procedures that are in need of improvement – it simply requires everyone to come together to analyse areas that truly require change.”

Dr W Malter is Head of Breast Cancer Centre Department at the University Hospital of Cologne, Germany, Department of Gynaecology and Obstetrics. Before this, he held the same position at Kliniken Essen Mitte, Germany. He has focused on gynaecological oncology. Oncology.

What is breast CT? And what are the benefits?

These are two questions the experts at AB-CT, the team behind the world's first spiral breast CT system, come across on a regular basis. In case you are asking the same questions – here are the answers.

A disruptive technology for clinical excellence

Breast CT, more precisely spiral breast CT (commercialised under the brand name nu:view), is a disruptive technology that is destined to change the breast imaging world. With excellent image resolution, suberb soft tissue differentiation and short scan times at low dose, it combines the benefits of conventional modalities in one system, providing a valuable tool for diagnostic breast imaging. The CE-marked scanner that is made in Germany is already in use on patients in Europe.

Enhanced patient comfort

Developed with the highest level of patient comfort in mind, nu:view allows for the patient to lie prone on the scanner table during the examination process, with the breast to be examined conveniently placed into the aperture. No compression is applied – making the entire process pain-free and helping that little extra for patients to feel reassured in a situation that may generally perceived as highly distressing.

The scan parameters are adjustable to accommodate various clinical requirements and patient types. There are no restrictions regarding age or gender. Even patients with dense breast tissue or patients with implants are able to experience the comfort, convenience, and peace of mind nu:view offers.

The gentle examination procedure makes breast CT also suitable for post-op follow-ups. Advanced visualisation techniques such as 3D volume rendering make the 3D high isotropic resolution images also a vested option for surgery planning. As the acquisitions are made with the breast in its natural shape, the three-dimensional images can provide information about the exact location of depicted lesions.

Single photon counting detector

Featuring state-of-the-art technology, nu:view provides images of the breast in true isotropic 3D resolution. Unlike conventional scintillation, nu:view uses a single photon counting detector based on cadmium telluride (CdTe) that converts x-rays directly into electrical signals. In the course of one rotation around the breast, up to 2,000 projection images are created – with a full spiral scan taking as little as 7 to 12 seconds, keeping dose levels low.

Efficient workflows

Thanks to its RIS/PACS integration capabilities (DICOM), the cutting-edge breast CT also provides efficient support for seamless workflows. And with no custom viewer required, radiologists can continue working in their familiar reading environment.

About AB-CT – Advanced Breast-CT GmbH

AB-CT is a pioneering medical technology company in the field of quality diagnostic breast imaging. With nu:view, their expert team of genius software engineers, design engineers, and medical physicists did not just develop another CT device, but a disruptive technology designed to leverage clinical excellence and empower radiologists all over the world to diagnose breast cancer at the earliest possible stage.

Challenges in brain tumour segmentation under scope

Neuroradiologist Dr Sofie Van Cauter described the challenges to brain tumour image segmentation during the European Society of Medical Imaging Informatics (EuSoMII) annual meeting in Valencia. She also outlined how, when clinically validated, AI could help tackle such problems.

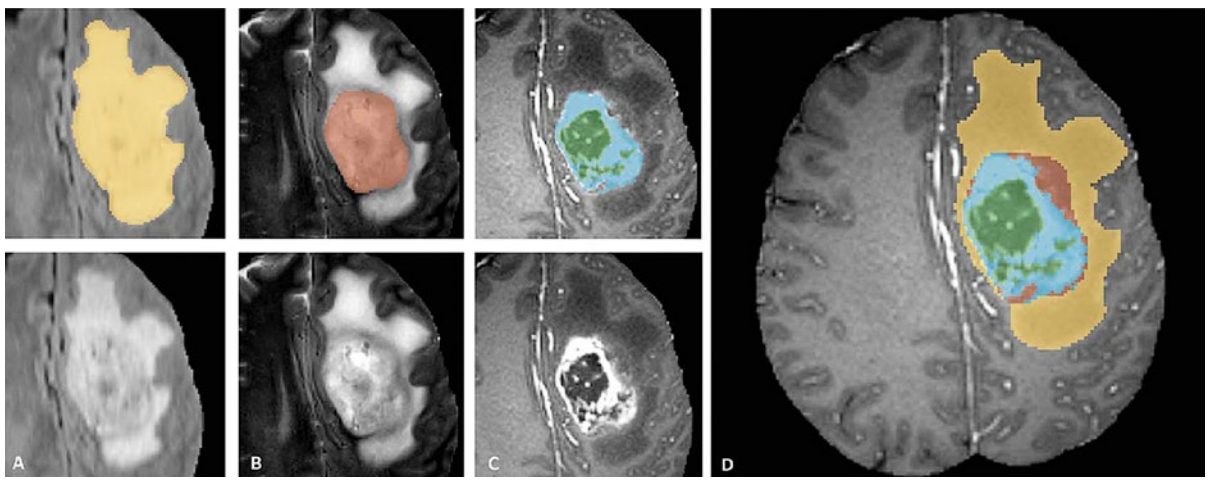
Report: Mélisande Rouger

The WHO classification of brain tumours has come a long way since first introduced in 1979. The 2016 classification was something quite revolutionary, neuroradiologist Dr Sofie Van Cauter explained during the EuSoMII annual meeting. 'For the first time, molecular diagnostics were taken into account in the diagnosis of brain tumours, leading to more detailed diagnoses and better reflecting the aggressiveness of the lesion and the patient's prognosis and response to therapy,' she said. 'This has been made possible with the evolution of next generation sequencing.'

In her talk, Van Cauter focused on primary brain tumours and especially gliomas, which are the most common type of brain tumours and come in different histological and molecular subtypes. In a first step, the pathologist determines the histological subtype and a grade of aggressiveness – the classic and still quite subjective, way to diagnosis. In the second step, as proposed by the WHO classification, several genetic mutations can be determined, leading to a more detailed final diagnosis.

Molecular diagnostics

'We know, since we applied molecular diagnostics, that we are much more able to predict the patient's prognosis and response to therapy. For example, in certain lesions a more benign histological subtype can initially be considered. However, if the lesion has a certain gene mutation, we know the lesion will have an aggressive course and the patient's prognosis is not good,' Van Cauter explained.



Typical segmentation of a tumoural lesion in the left frontal region as proposed by the BraTS consortium. Left Panel: A-B-C: whole tumour segmentation (yellow), segmentation of the tumour core (orange), the enhancing tumour portions (blue) and the necrotic core (green). Right panel: the different labels put on one anatomical image. Adapted from Menze et al. IEEE 2015.

When dealing with a brain tumour, radiologists look at multiple MRI sequences performed in multimodal imaging protocol. In recent years, neuro-oncology research has focused on advanced MRI techniques, which try to relate histological features in radiological phenotypes, such as cellularity or vascularity. In current clinical practice, the basic imaging protocol consists of T1-weighted sequences, in which anatomy can be demonstrated, T2-weighted sequences, which relate to oedema and can be a measure of cellularity. There are also FLAIR sequences, to distinguish more subtle oedema, and T1 contrast-enhanced sequences, which distinguish areas with disrupted blood-brain barrier from regions of non-disrupted blood-brain barrier. Diffusion and perfusion-weighted sequences provide additional measures, reflecting vascular proliferation and cell density.

Challenges for brain tumour diagnosis and follow-up

When a glioma is suspected, and when dealing with a brain lesion on MRI, radiologists still try to make a diagnosis according to the histological subtype. However, this diagnosis is quite subjective, which is a major issue. 'Accurate, quantitative thresholds are not determined yet, we just base the diagnosis on qualitative, subjective features like "low-to-moderate oedema is probably reflecting this or that type of tumour". We still have a problem with the diagnostic accuracy to predict the histological subtype of a glioma – it's currently moderate to low. We hardly got started with the correlation between molecular profiling and imaging,' she pointed out.

Glioma therapy is a combination of surgery, chemo- and radiotherapy. There have been many efforts in more advanced therapy, but until now clinicians have stayed with the cornerstone of therapies established since 2005.

An even more important issue in glioma is follow-up, currently done according to the RANO criteria, which try to classify patients in a certain category, from complete response to partial response to stable disease in progression. 'This is done, again, in a very basic way. Just to classify into four categories, you need to sum the perpendicular diameters of all enhancing lesions and compare them to the smallest measurable tumour volumes. The classification only takes into account T1-weighted sequences with contrast administration and to a minor extent, features on T2 and FLAIR images,' Van Cauter explained.

Thus, radiologists face many challenges in adequate diagnosis and follow-up of gliomas. Evaluation of gliomas is subjective; does not take into account robust quantitative parameters and is not adapted to the emerging evolutions in molecular diagnostics.

'Molecular diagnosis is better suited, but is still a new and emerging field,' she pointed out.

AI will help, but needs clinical validation

AI entered neuro-oncology a few years ago. A Chinese group notably developed an AI algorithm that determined the subtype of brain tumours much faster and more accurately compared to a group of neurologists.

In radiology in general, the tasks in AI algorithms fall into three categories: detection, segmentation and classification. Segmentation algorithms consist of multiple steps. Lesions, or other tissue of interest, have to be diagnosed, delineated and finally, different tissue types must be determined. In the case of a brain tumour, solid tumour, necrotic core and oedema have to be separated from healthy tissue. The development of automatic segmentation algorithms that focus on these tasks is an enlarging field and in the last ten years, the number of publications has risen steeply.

For segmentation, convolutional neural networks are used, which consist of several steps and multiple layers in a computer algorithm, using features related to symmetry, intensity gradients, etc. These characteristics are combined to classify different regions as enhancing tumour, non-enhancing tumour, necrosis or oedema.

Until now, this work has stayed mainly in the field of engineering, signal and image processing. Using this kind of AI on a daily basis still requires multiple validation steps, from technical to biological and finally clinical validation. 'Today, even starting from the beginning of the validation steps, we still have some limitations,' she said.

The first, very important technical limitation is scarcity of data. The first general public studies on AI used data sets of 60,000 images or more, whereas in the medical field we have to work with smaller data sets – mostly between 100 and 1,000.

Then, brain tumours are very heterogeneous – each is different

Can imaging progress AD therapy studies?

Alzheimer's research: A lost century

Lack of understanding around Alzheimer's disease (AD) has significantly slowed advances in the treatment of this incurable condition. Imaging has proved to be reliable in differentiating between AD and other forms of dementia, and its contribution will continue to help develop profiling, an increasingly interesting approach for the development of new and more efficient drugs, according to Sven Haller, a Swiss neuroradiologist, who spoke during EuSoMIIs annual meeting, held last October in Valencia, Spain.

Report: Mélisande Rouger

Over a century of research in AD treatment has failed to cure people. For this, there are two main reasons, according to Haller, who will chair the New Horizons session on 'Alzheimer's disease and neurodegeneration: visualising the invisible' during this year's European Congress of Radiology (ECR).

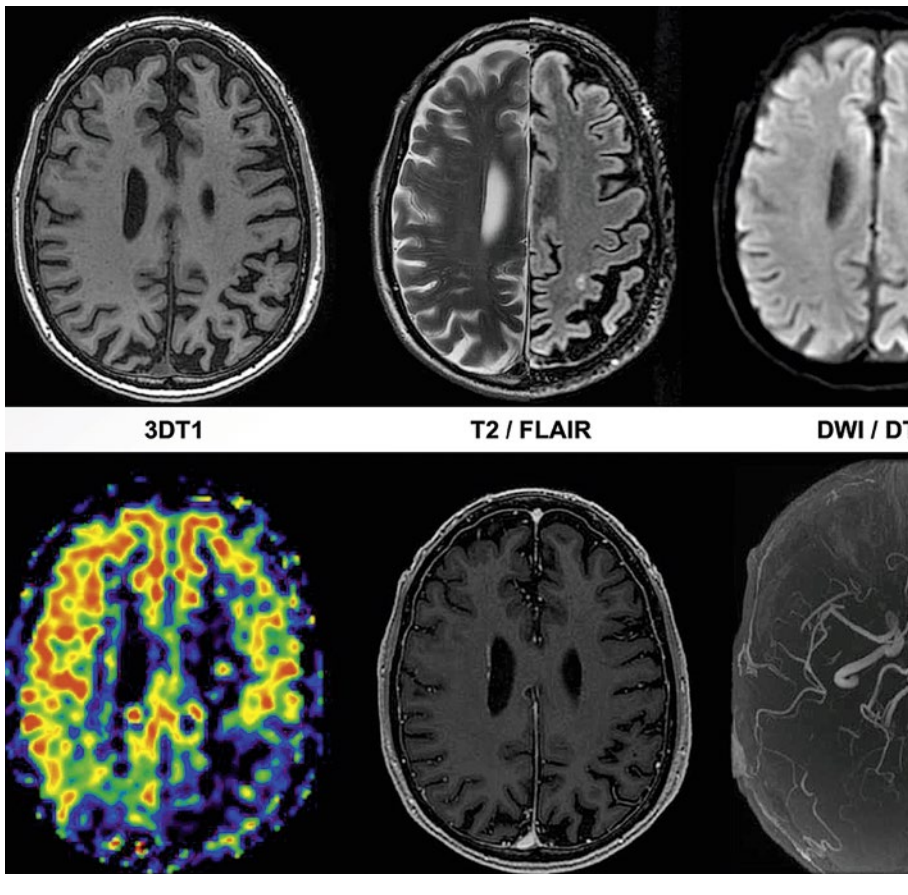
'Giving therapy to only patients with clinical symptoms of dementia has greatly impacted on therapeutic advances. For 80 years, we've given drugs to patients who already had symptoms. However, we know that if we wait for symptoms to develop, by then 50% of the neurons are lost. This was already confirmed in a study from 1968 *(Tomlinson BE, Blessed G, Roth M (1968) Observations on the brains of non-demented old people. J Neurol Sci: 7:331-356.1)*.Even if the medication works, it will very likely not revitalise dead neurons,' he explained.

Another major setback has been the profound misunderstanding of Alzheimer's disease, which is a form of dementia. There are many types of dementia, for example vascular dementia, a group of frontal dementias and Lewy Body dementia, among others. Alzheimer's and dementia are not the same, but they are commonly perceived as such, Haller pointed out. 'You don't have one stereotypical form of dementia. Not everybody who has dementia has AD. If you simply treat a person with signs of cognitive decline with AD medication, it may just not work, as this patient may not have Alzheimer's disease,' he said.

Imaging central to early diagnosis and differentiating

To complicate matters further, there are also different disease subgroups of AD, which must be tackled independently. Drug development must take this diversity into account, because there will not be 'a magic universal drug that will work in all patients with dementia,' he stressed. Medical imaging is needed for early and specific identification of patients at risk of a specific type of dementia before the onset of clinical symptoms.

Imaging is a great way of assessing and differentiating dementia, which can further help to develop adequate medication for each dis-



Multiparametric MR protocol allowing for the assessment of brain structure and atrophy, various markers of neurovascular diseases and functional brain perfusion in one single imaging session

Dr Sofie Van Cauter is a neuroradiologist at Ziekenhuis Oost Limburg in Genk and University Hospitals Leuven, Belgium. To gain her PhD, she researched advanced MRI techniques in gliomas with an emphasis on diffusion kurtosis imaging, MR spectroscopy and perfusion techniques. This was done in collaboration with the department of Electrical Engineering of the Catholic University Leuven, where she researched deep learning techniques in diagnosis and follow-up of gliomas.

in size, shape and location. Tumour boundaries are often unclear or irregular, with discontinuities. In addition, hospitals all have different scanners and image protocols, which complicates standardisation and data quality.

Nonetheless, there has been some progress, especially with the Brain Tumour Segmentation Challenge (BraTS), an objective evaluation of the different state-of-the-art methods that offers publicly available data sets and a community benchmark. BraTS is a data set of more than 500 cases, from different scanners, centres and imaging protocols, and also provides additional clinical data on overall survival as well as an extra assessment of uncertainty in brain tumour segmentation.

'This has been a tremendous evolution in the field of engineering to face the challenges of the technical validation, the first step of getting brain tumour segmentation into a validated clinical product,' van Cauter said.

Investing in interoperability, trust and safety

The next step is biological validation. 'We still have a problem

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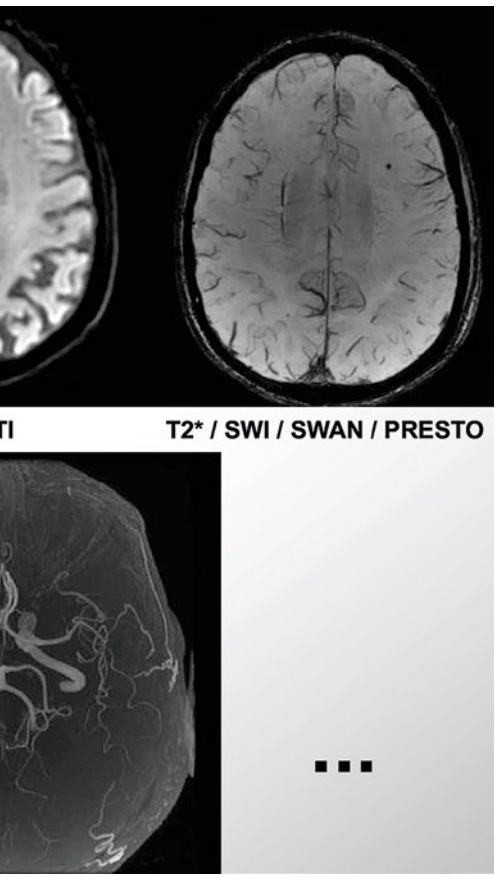


there and it mainly relates to the way engineers and medical doctors communicate and, of course, how brain tumours biologically behave. Images are not biological entities. With glioblastomas, neurosurgeons can remove everything and two months later we have a new tumour lesion. Microscopic tumour invasion cannot be captured either by imaging or by AI. When we segment tumours, an active tumour, in the language of engineers, is regarded as an enhancing tumour - and that is just not true. Lower grade tumour parts in glioblastomas are often non-enhancing,' she added.

Clinical validation goes beyond the pure act of segmentation. The final aim is to adapt these algorithms to answer the current clinical and radiological challenges as stated, more reliably than current clinical practice. 'If we think about segmentation,' she said, 'I think the targets are: stepping up to molecular diagnostics, detailed treatment planning, volumetric therapy follow-up and more detailed evaluation and early prediction of overall survival.'

AI in medical data analysis and neuro-oncology is here to stay and from the technical point of view, results are getting quite reliable. But to be introduced in the clinical setting, future investment should be in interpretability, trust and safety. 'Some algorithms are able to make extremely accurate predictions but, from a clinical point of view, how can we trust predictions of features we can't understand? We need to invest more in biological and clinical validation of techniques.'

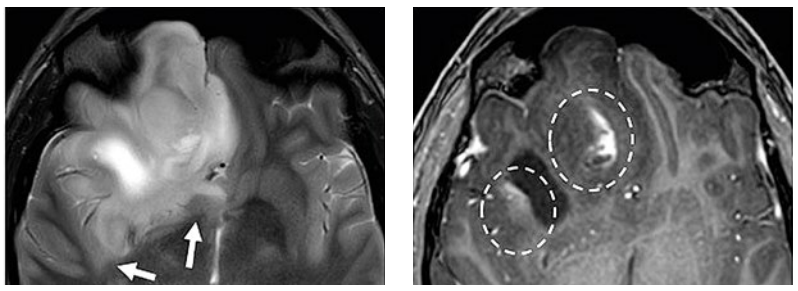


Illustration of a complex tumoural lesion in the right frontal lobe. The technical segmentation entities (oedema, non-enhancing tumour or tumour core, enhancing tumour and necrosis) are difficult to distinguish in this example. Notice the irregular, ill-defined tumour borders (arrows – left image) and the faint contrast enhancement (dashed circles – right image). These are possible hurdles for automatic segmentation algorithms.

Setting the standard for quality assurance in X-ray imaging

Finding simple but powerful QA solutions

Fredrik Ljungberg is president of RTI, a Swedish firm that develops solutions for X-ray quality assurance (QA). During our European Hospital interview, he explained the levels reached in QA and future aspirations of this already world-leading QA company.

Interview: Daniela Zimmermann

Diagnostic radiology demands diverse and top quality medical imaging technology. Among the equipment used, the importance of X-ray QA (quality assurance) remains paramount to control X-ray radiation.

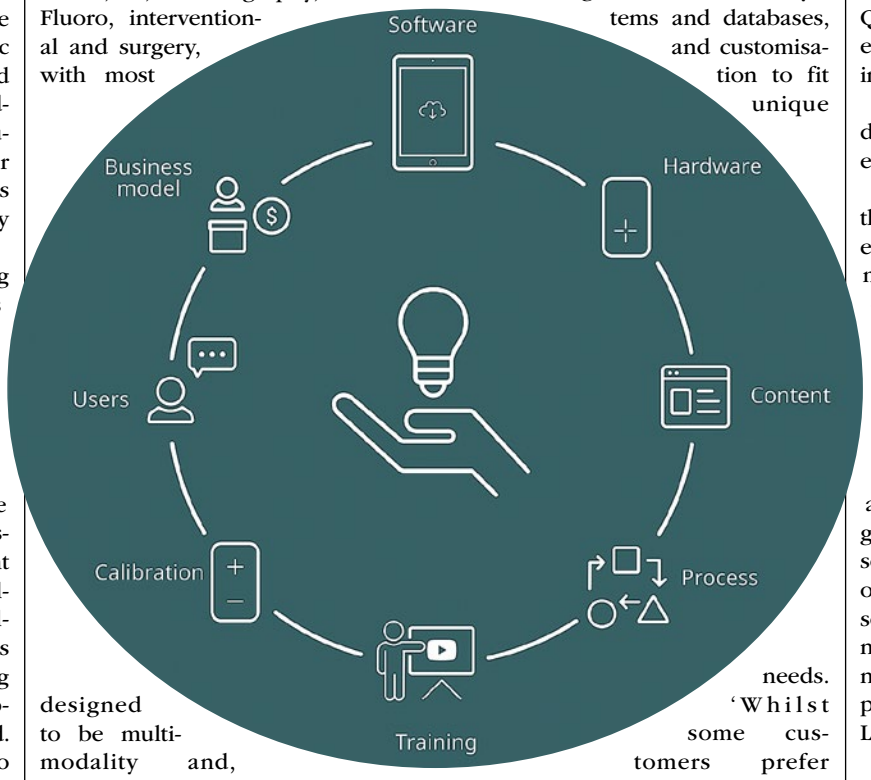
Since 1981, when RTI invented the first X-ray QA system for diagnostic radiology, the firm has invested heavily in R&D, and became a world-leading manufacturer of QA solutions. By rebranding in December 2019, the company expressed its vision to 'set the standard for quality assurance in X-ray imaging'.

Thus, RTI will continue a strong focus on QA solutions to address customer needs in a broader sense, with a specific emphasis on customer collaboration, workflow automation, traceability and compliance within its dedicated software solutions.

The objective is also to include attention to detail on training, customer care, continued investment in R&D and the role artificial intelligence (AI) will play. 'Our collaborative approach to customers includes all processes; from eliciting needs and R&D, to training and support,' Fredrik Ljungberg confirmed. 'To understand needs, we seek to engage in long-term cooperation with customers to understand what they want to accomplish: the starting point should always be their goals and what they plan to do to be successful.

'We are trying to take a more overall view of this because, historically in this industry, the focus has been on technical features and devices. Once you understand this, you can create a solution that not only meets the need but also fits into the customer context. The solution needs to be simple, yet powerful.'

RTI's X-Ray QA portfolio provides dedicated kits and accessories for dental, CT, mammography, Rad/Fluoro, interventional and surgery, with most designed to be multi-modality and, combined with Ocean software, to provide simple-to-use features for routine inspection, through to highly customisable QA programs for deep analysis and record keeping.



The QA solutions are used worldwide by hospitals, manufacturers of X-ray equipment such as GE and Hologic, service providers and government authorities, across all modalities.

Ljungberg emphasised the importance of change to achieve improvements and efficiency gains, as well as the role of training. He also envisioned a shift from managing QA measurements manually, in Excel, towards a dedicated QA software, with a software suite that strongly emphasises workflow automation and compliance, as well as enabling the integration with other systems and databases, and customisation to fit unique needs. 'Whilst some customers prefer web-based training, others want to gather staff for classroom training. In other cases, we do customisations to align with a QA process and integrations to feed data to and from other systems. In general, the more you invest in training and customisations, the more value you get.' Ljungberg outlined a strategy to set the standard for QA in X-ray imaging. 'We've been around for 40 years and believe in niche and focus,' he explained. 'Within the area of X-ray QA for diagnostic, we believe in offering solutions to all QA needs, ranging from instruments and software applications to training and different business models.

'To be really successful, the customer needs a solution; the hardware device is only one part of that solution. We also believe software is the key to success. Managing your QA manually, or using Excel, may be easy short-term, but expect no major improvements.'

Taking out the human element delivers consistency and helps to eradicate errors.

'In our software, we seek to hide the complexity to make complex easy,' he explained, adding: 'Another main component of our strategy is our collaborative approach to customers and partners.'

Since inventing the solid-state meter in the early 1980s, RTI's attention has changed from hardware meters and technical capabilities to QA solutions in general and software in particular. 'I see general trends from hardware to software because more and more of the customer value is with the software. It is not that hardware is not important because, if you do not have the hardware you cannot provide the value in the software,' Ljungberg reasoned.

'Today we offer a unique solution for all QA needs in diagnostics. For example, you can implement a standardised process in a workflow, automate certain steps to gain efficiency, and get full traceability.'

RTI remains reluctant to discontinue products and maintains that it always offers upgrade paths and adopts a customer flexible and focused approach with high-quality support. 'To become even more effective, customers may want to implement a standardised QA process and to feed data from their QA to and from other systems. Some may want to buy the equipment, whilst others prefer leasing. There are many different needs to address. The goal of our solution is to address all those needs, so we can provide the best solution for each individual customer,' Ljungberg added.

There is also emphasis on integration of RTI's software into existing databases and systems. 'Software and data integration is becoming more common,' he said. 'It is part of the digitisation of the QA process. Customers want to be effective and that requires automation and integration.'

Ljungberg believes AI will play an increasingly important role in RTI's data-driven systems in the future. 'AI algorithms are very good at analysing large amounts of data and making conclusions and recommendations. This way, we think the efficiency and value of the software will be even higher in the future.'

Fredrik Ljungberg is President at RTI Group, a leading developer of X-ray diagnostics QA hard- and software in Sweden. He is also co-founder, former CEO and current board member of several companies, including Diadrom, a provider of diagnostics and autonomous driving solutions, and share registry tech company Reguity. A trained researcher in applied IT, Ljungberg has been Professor at Göteborg University and published more than 50 scientific papers and several books on the topic.

Safety for patients and health benefits for personnel

'get up' – the swivelling supp for radiology

Febromed GmbH & Co. KG, the expert in delivery room equipment and medical accessories from Oelde, Germany, has developed 'get up', an innovative handle system for radiology. The new swivelling system was installed for the first time in a state-of-the-art CT scan room at the Institute of Diagnostic and Interventional Radiology and Neuroradiology at Essen University Hospital.

For a secure grip

Many patients find getting onto the examination table for a CT scan difficult. In particular, restricted mobility leads to uncertainty as the patient is positioned and arranged, thus placing increased physical strain on care personnel, predominately in the back area. The new 'get up' handle system from Febromed offers a solution: this swivelling system helps patients get onto the table before their scan and stand up again safely and comfortably afterwards. It minimises the risk of falling and provides a secure grip. It helps personnel by reducing the physical strain of their job. As a result, the organisation as a whole benefits: since the actual physical strain on personnel is significantly reduced, employee sick leave due to back pain is also minimised.

Positive experiences

After installing the handle system in May 2017, the Institute of Diagnostic and Interventional Radiology and Neuroradiology at Essen University Hospital has consistently had positive experiences. As Anton S. Quinsten, Senior radiographer, reports, 'We are really happy with the "get up" system from Febromed. The first few months have shown that the handle system is considered a real asset by both patients and personnel.'

Space-saving and durable

The 'get up' handle system is designed for space-saving mounting on the ceiling and can be swivelled by 360°. The structure can be locked in 15° increments so that the system

Alzheimer's research: A lost century

Continued from page 25

which is a marker of neurodegeneration; perfusion, a marker of brain function, and a different range of markers of vascular disease.'

Imaging is very useful to diagnose patients with mild cognitive impairment (MCI) at an early stage. However, this is not enough. 'Approximately half of unselected MCI will remain stable even without intervention,' Haller explained. 'In the MCI group, you must detect those who will likely deteriorate later on.'

The typical pharmaceutical trial including unselected MCI cases will include approximately 50% of stable MCI patients, half of whom will get placebo and the other half will receive treatment. 'This means only 25% of MCI cases will progress and get the true medication, while 25% of MCI cases remain stable despite being in the placebo group. That's one of the many reasons it's so difficult to detect a treatment effect.

Appeal for a more faceted approach

Most studies focus on hippocampal atrophy alone, the known imaging hallmark of dementia. However, hippocampal atrophy is not specific to AD – it also occurs in other types of dementia, e.g. frontal dementia. And not all cases with a mild degree of hippocampal atrophy will develop dementia. 'We should therefore include the assessment of the entire pattern of atrophy of the whole-brain, which is much more specific than looking only at the hippocampus. Moreover,' Haller added, 'we should add into the equation markers of vascular disease, brain function etc., as discussed above.'

Radiologists should watch out for the obvious. Intuitively it is obvious to assume a linear correlation between more atrophy and worse clinical symptoms. However, in reality it is much more complex.' There is a cognitive reserve or brain reserve. The same amount of measurable atrophy may be associated with a very large variability of cognitive decline at the individual level, depending on the cognitive reserve, social integration, education, activity in daily life, nutrition etc.

A complex situation

'We should not simply assume that a case with, for example, moderate hippocampal atrophy will inevitably also have moderate clinical symptoms of dementia. The situation is significantly more complex.

Early diagnosis is key and profiling is an interesting strategy. Ongoing European trials run tests to assess risk factors, family history and genetics for preselection of high-risk people for drug trials, for example the European Prevention of Alzheimer's Dementia Consortium (EPAD). Haller: 'A lot of work remains to be done, but if efforts are put to good use and properly targeted, we could make big leaps in AD and dementia treatment in the near future.'

Sven Haller, visiting professor at the University of Uppsala, Sweden, and neuroradiologist at the Centre d'Imagerie Rive Droite (CIRD) in Geneva, Switzerland, follows a special interest in advanced neuro-imaging techniques, particularly advanced MR techniques including functional MRI, real-time functional MRI neurofeedback and arterial spin labelling (ASL), notably in the domain of neurodegenerative and neurovascular diseases.
His scientific awards include the Lucien Appel Prize and many more.
He is also section editor for advanced imaging in Neuroradiology, the official journal of most European Societies of Neuroradiology, and section editor for neurodegeneration in the new textbook of Neuroradiology from the European Society of Neuroradiology.

ort system

is always in the optimal position for the patient. This purely mechanical construction ensures easy handling and extended durability.

Close surveillance is mandatory for IB development

‘Imaging biomarkers and AI are the new drugs’

Report: Mélisande Rouger

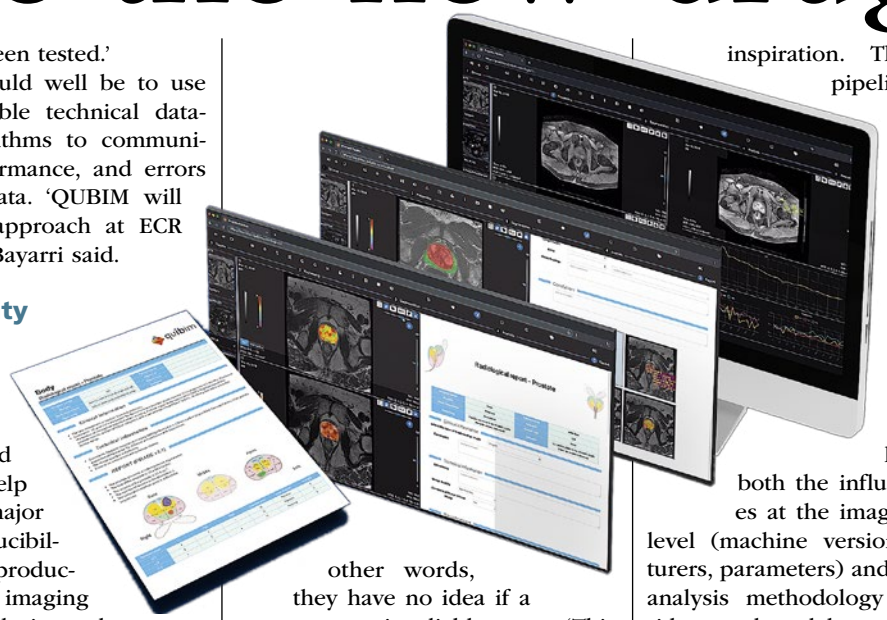
Imaging biomarkers (IB) have advanced tremendously since first described 25 years ago, but many challenges still block their widespread use. During the EuSoMII’s annual meeting in Valencia, Dr Ángel Alberich-Bayarri gave pragmatic solutions to tackle current bottlenecks and explained why close surveillance is mandatory for further development of IB, which, along with AI, is the new drug. However, these need close surveillance with properly reported results.

‘New drugs need strict evaluation phases in the form of clinical trials and be approved by regulatory bodies to reach the market,’ he advised. ‘Even after being approved, a close surveillance of safety, effectiveness and efficacy is performed in a large number of patients,’ he pointed out. ‘We have to adopt a similar structure for IB and AI; if we are structured in therapy design and development, we also should be good in detection and diagnosis. Technical sheets of any drug specify where the drugs work better, or in which population they have not been tested.’

A solution could well be to use publicly accessible technical datasheets of algorithms to communicate their performance, and errors in real-world data. ‘QUBIM will showcase this approach at ECR 2020,’ Alberich-Bayarri said.

Reproducibility crisis

Having information on a measurement’s performance and failure could help to solve the major issue of reproducibility. ‘There’s a reproducibility crisis in imaging biomarkers analysis and AI algorithms. We use many tools from different resources, in different hospitals and environments,’ he added. ‘We don’t know which tool is best.’



Radiologists cannot evaluate even the simplest measurements currently available. They don’t have a single value on what Alberich-Bayarri called the ‘confidence interval’. In other words, they have no idea if a measurement is reliable or not. ‘This is quite surprising, because even for a simple thermometer, we will find the confidence or the uncertainty of measurements performed with that device. So, he pointed out, ‘We urgently need a methodology philosophy for imaging biomarkers.

The EIBALL’s statement paper on the validation of biomarkers might be a proposal from which to draw inspiration. The validation pipeline is mainly focused on checking an algorithm’s precision, accuracy and clinical validity with the clinical outcomes.

Precision is easy to evaluate by looking at both the influence of biases at the image acquisition level (machine versions, manufacturers, parameters) and at the image analysis methodology level (algorithms and models used).

Accuracy can be assessed by comparing a biomarker with solutions that have demonstrated their reliability, for example concentrations or different properties, and of course pathology, by comparing results of a measurement with a sample’s real value. ‘However, we must assume that sometimes we will not be able to measure accuracy because of the lack of ground truth,’ Alberich-Bayarri said.

Clinical validity of an algorithm can be measured not only in the short term, by evaluating diagnostic and therapeutic problems, but also in the long term, i.e. finding biomarkers with a prognostic value.

Manual interaction with client-server solutions or workstations is a bottleneck for IB widespread use. A solution is to use a rules engine to execute specific AI image analysis fragment and imaging biomarkers analysis pipeline. In any case we have to keep humans in the loop. ‘Even if the pipeline is completely automated, it must incorporate checkpoints for user interaction,’ he advised.

Computational resources have to be ready for massive analysis of imaging biomarkers, and one strategy is to design and implement high performance computing elastic infrastructures after the necessary stress tests, evaluating analysis times and reports delivery with a high number of cases to be analysed.

Structured reporting

There are several solutions to integrate IB with structured reporting (SR), which is another current difficulty. ‘We can combine AI algorithms, imaging biomarkers analysis and structured reporting in same environment,’ said Alberich-Bayarri, who has developed a CE marked architecture capable of hosting and

Developing AI algorithms for earlier detection

Assessment of treatment response to glioblastoma

Novel advanced imaging biomarkers are being developed in a series of studies at several UK centres that may lead to the earlier assessment of treatment response to glioblastoma (GBM) and a better survival rate.

Report: Mark Nicholls

Through a number of clinical trials – and the application of artificial intelligence (AI) to retrospective data sets – the aim is to highlight approaches that will enable clinicians to recognise much sooner when treatments are failing and thus switch patients to a second therapy before too late.

Neuroradiologist Shah Islam, a clinical research fellow at Imperial college London (ICL), who is completing a PhD in advanced computational brain imaging, has become a key figure in the research to develop the robust imaging biomarkers needed to detect early treatment response in glioblastoma cases. ‘The aim is to see whether, by using the novel MRI sequence, we can predict which patients will respond to treatment at the mid-radiotherapy stage,’ he said.

Among the trials is the Diffusion in Glioma Study (DIG), in association with the Brain Tumour Charity. This involves five UK neuroscience centres – Charing Cross Hospital, London; Addenbrooke’s Hospital, Cambridge; The Royal Infirmary, Edinburgh; the Walton Centre, Liverpool, and the National Hospital for Neurology and Neurosurgery at Queen Square, London – where advanced Diffusion Weighted Imaging (DWI) MRI sequences are performed at three time points: pre-, mid- and post-radiotherapy.

With current imaging reliance on T1 contrast enhancement to look for disease, the researchers are unsure whether this is sensitive enough to appreciate subtle changes in the underlying tumour.

This has seen use of advanced DWI to extrapolate the most sensitive part of diffusion imaging that can help researchers to accurately identify changes in the tumour microenvironment.

‘What is important about the DIG study is that it is multi-centre and uses scanners from multiple manufacturers, making any positive results more robust,’ said Islam.

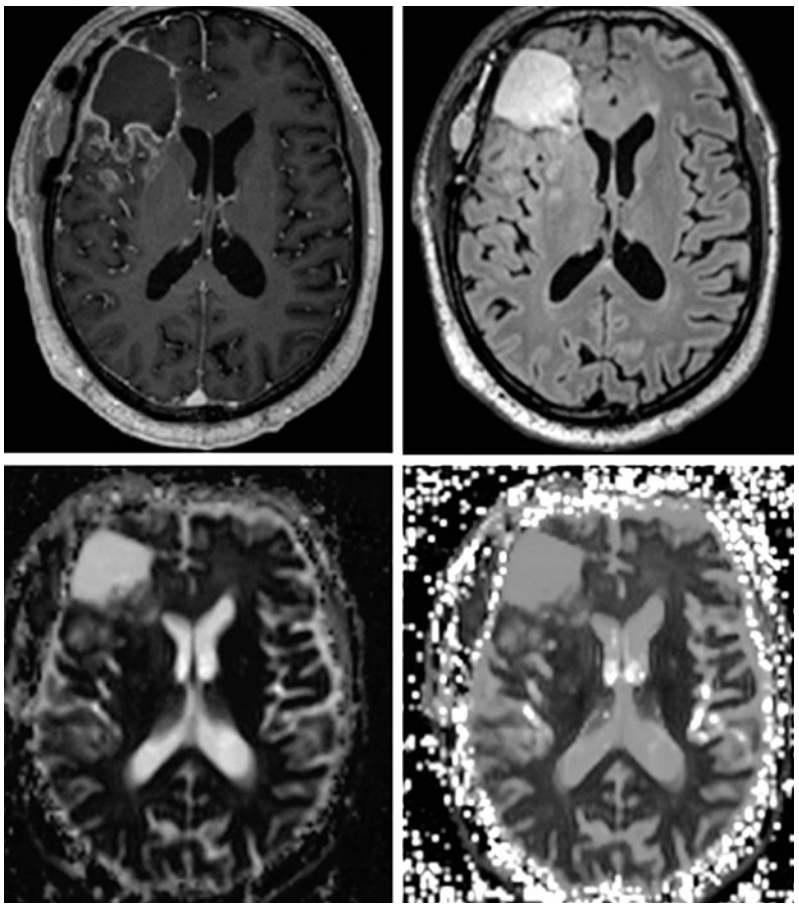
A second study – the ^{18}F FPIA PET MRI in Glioma, funded by the Medical Research Council – uses a new radio tracer developed at Imperial College London combined with hybrid PET/MRI scanning. ‘The radio tracer has been developed to specifically detect tumour cells in the brain, by looking for fatty acid metabolism, which healthy brain cells do not exhibit,’ Islam explained. ‘The idea is that we can look for any residual disease following the surgical resection, and also explore its use as treatment response marker following radiotherapy.’

As ^{18}F FPIA is designed to detect only tumour cells, the healthy brain should not demonstrate any signal.

Islam is also on the steering committee of the Tessa Jowell* Brain Matrix (TJBM) – a 10-centre government-led study aimed at improving outcomes in patients with aggressive brain tumours – which endeavours to curate all GBM data prospectively, including imaging data, histological and molecular data, and genetic data, to allow the successful development of an AI approach.

‘The lifeblood of any AI in imaging,’ Islam continued, ‘is the data used to create algorithms. With the TJBM, we have the volume of data coming through, which is labelled perfectly and combined with patient metadata. This will allow us to develop AI algorithms that can detect treatment response earlier.’

A current problem when patients go on first-line treatment for GBM – surgery, radiotherapy and adjuvant temozolomide (chemotherapy drug) – is that clinicians do not know which patients will do well or won’t until it is too late. ‘There is a small window to change peo-



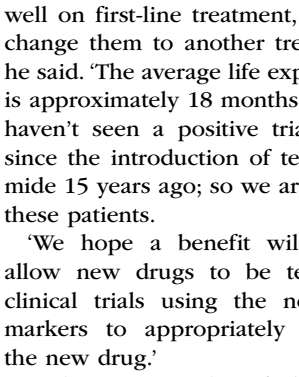
Top left: T1 weighted MRI of a patient with a recently resected right frontal MRI.
Top right: Fluid-attenuated inversion recovery (FLAIR) MRI of the same patient.
Bottom left: ADC map created from standard diffusion sequences.
Bottom right: DDC map created from multi b value, advanced diffusion sequences

Ángel Alberich-Bayarri PhD is the CEO of QUIBIM, a company that applies AI and advances computational models to radiological images to measure changes produced by a lesion or pharmacological treatment, offering quantitative information to radiology.

integrating all these elements for prostate applications.

The main goal is to avoid workflow interruption and to be prepared for massive analysis computing performance. 'Using these types of architecture,' he said, 'our main aim is to convert our radiology department into a quantitative radiology department, where all biomarkers are seamlessly extracted.'

Radiologists will not manage to integrate SR with quantitative imaging if SR is independent from the user and biomarker's interface. 'Radiologists,' he concluded, 'want the SR integrated with AI and biomarkers. So we have to think of changing our current paradigm.'



Neuroradiologist **Dr Shah Islam**, who runs the DIG and FPIA studies, is a clinical research fellow at Imperial College London. Having graduated from Barts and The London School of Medicine and Dentistry, he underwent combined clinical academic training at Barts and was an NIHR academic clinical fellow in Radiology at The Royal Marsden NHS Foundation Trust. His research focuses on developing novel imaging biomarkers to detect early treatment response in glioblastoma using advanced imaging techniques achieved through a number of clinical trials and advanced computational methods involving AI.

ple to second- line therapies; if we can identify those that won't do well on first-line treatment, we can change them to another treatment,' he said. 'The average life expectancy is approximately 18 months and we haven't seen a positive trial result since the introduction of temozolomide 15 years ago; so we are failing these patients.

'We hope a benefit will be to allow new drugs to be tested in clinical trials using the new biomarkers to appropriately validate the new drug.'

Preliminary results of the trials were presented at RSNA 19, but Islam confirmed that they are still a long way from clinical translation into routine imaging.

* Baroness Tessa Jowell was a UK politician who died of GBM and worked to raise awareness of the condition.

On the way: specific AI apps to scan children

The future of paediatric imaging

A premature infant with sepsis and the tiniest veins receives precisely targeted, lifesaving medications intravenously. A teen cyclist collides with a car; his head is hit; minutes later attending medics know there is bleeding in the brain. Thanks to advances in medical imaging, paediatric patients are receiving faster, more accurate diagnoses, quicker treatments, and experiencing better outcomes, says Dr Diku Mandavia, chief medical officer for Fujifilm Medical Systems in the USA and Fujifilm SonoSite Inc.

While providers continue to adhere to safe, low-dose imaging protocols, we are also seeing a trend toward finding new care pathways that use ionising-free modalities. For example, more clinicians are opting to use point-of-care ultrasound over CT to diagnose appendicitis in children because it's safer and has a very high accuracy rate. Many paediatric emergency physicians are adopting an ultrasound-first philosophy because it delivers a speedier diagnosis. It's also less costly, safer, painless, and because children typically have low body fat, it's easy to acquire very clear images with ultrasound.

Neonatal and paediatric intensive care units are adopting dedicated imaging equipment, such as wireless, portable DR and point-of-care ultrasound, so that children can be diagnosed more quickly and avoid being moved around the hospital, where they risk exposure to potential nosocomial infections.

New technologies are also aiming to reduce the need for sedation during paediatric imaging, making exams safer. In terms of design, reducing patient anxiety is a top priority. That means smaller, less noisy, more soothing equipment that acquires images faster and reduces the need for the patient to stay still.

There are also important social factors for imaging children. Since paediatric patients are not always able to speak up for themselves, radiology is in a unique position to uncover adverse life events, such as physical abuse. Historically, hospitals sometimes use double density CR films to conduct skeleton surveys to detect abuse – requiring as much as 20 films on a 9-month-old. With new advances in digital radiography systems, physicians can detect evidence of abuse in the bones with lower dose exposure.

Healthcare IT and artificial intelligence

While it is always important to have a comprehensive picture of the patient, it is particularly vital in paediatrics. First, young children lack the verbal skills to provide any kind of history. Moreover, many very sick children begin treatment at a community hospital, but need to be transferred to a children's hospital – their imaging should be immediately accessible to the new clinical team.

New advances in healthcare IT and enterprise imaging will drive better care and outcomes for paediatric patients. Sharing of imaging data needs to be seamless. This capability reduces the need for repeat exams in children and thereby minimises their exposure to excessive radiation.

Artificial intelligence has the potential to revolutionise paediatric care. Boston Children's Hospital helped develop and is using a decision support platform to improve the accuracy of paediatric brain scans.

Children's brains change at a rapid rate, so accuracy is vital. The deep-learning tool that reviews thousands of previous scans is helping clinicians to pinpoint the exact diagnosis. In the future, we will see many new AI applications specific to paediatric imaging.

A profession in need of a boost

One unfortunate trend is the lack of young residents seeking to pursue the paediatric radiology subspecialty. Moreover, a recent survey of members of the Society for Paediatric Radiology found that today's paediatric radiologists suffer from significant burnout, with 66 percent of respondents reporting high levels of emotional exhaustion.

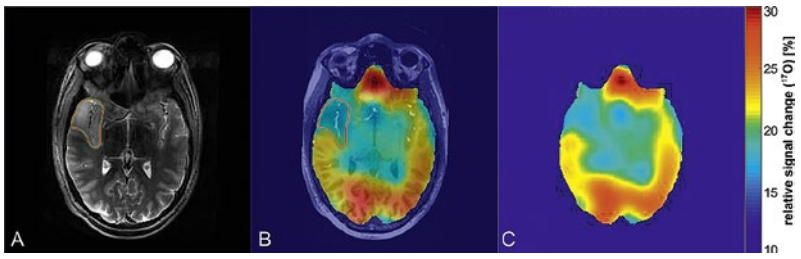
While imaging technology will continue to evolve, it is imperative that the medical profession find ways to revive interest in the subspecialty, and recruit and retain the best and the brightest. High tech will never trump human touch. The future of paediatric imaging depends not only on technological advances, but most importantly, on the people who put those tools to use.

X-Nuclei MRI

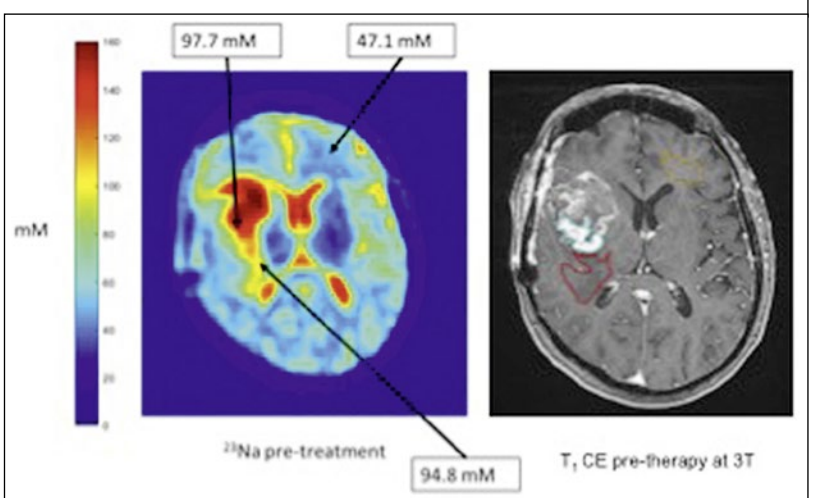
Oxygen provides insights into tumour metabolism

Report: Sascha Keutel

Magnetic resonance imaging (MRI) usually measures the magnetic moment of the hydrogen atomic nuclei arising from the spin. However, scientists at the German Cancer Research Centre (DKFZ) are investigating the spin of other nuclei for imaging: 'X-nuclei imaging has a large potential for MRI imaging as the x-nuclei play an important part in many physiological processes,' according to doctor and physicist Daniel Paech MD, (Dipl. Phys). 'For instance, we have been able to show that it is possible to measure oxygen-17 in the healthy brain and in brain tumour tissue and to gain information about the tumour's metabolism.'



7 Tesla Oxygen-17 ($^{17}O_2$) MRI: Images show transverse slices of a subject with low-grade astrocytoma (WHO grade 2). A: T2-TSE, B: Fusion of a T1-MPRAGE image with $^{17}O_2$ MRI; the red line marks the tumour area based on the extent on the T2-TSE. C: Native $^{17}O_2$ image. In accordance with the Warburg effect, the $^{17}O_2$ image shows reduced oxygen consumption in the tumour area.



7-Tesla Sodium-MRI in a subject with histologically secured glioblastoma (WHO grade 4). The quantitative sodium contrast (left) shows increased natrium concentrations in the tumour area with blood-brain barrier disruption and peritumoral oedema. Right: Clinical reference image, T1-MPRAGE with contrast medium. The reference image shows the regions analysed in colour (blue: tumour with blood-brain barrier disruption, red: peritumoral oedema, yellow: contralateral white matter).

The oxygen we breathe via air is mainly isotope oxygen-16. It has no magnetic moment, which is why it cannot be measured in an MRI scanner. The stable, non-radioactive oxygen-17 ($^{17}O_2$) is also found but in smaller concentrations. To visualise the oxygen-dependent metabolism in the human body, such as for MRI examinations, or for dynamic inhalation experiments, the patient needs to inhale it in enriched form. Wherever oxygen is metabolised in the tissue, $^{17}O_2$ combines with hydrogen. This makes it detectable in the MRI scanner's magnetic field. Tissue which metabolises a lot of oxygen shows up as lighter on the image. The radiologist would still be able to obtain an image without inhalation, but with poor resolution and without information on metabolic activity.

'The exciting thing for us is that oxygen-17 can only be measured in its water-bound form, but not in haemoglobin-bound form. As oxygen is only consumed in one place in the body, i.e. at the mitochondrial membrane in the cells for energy production in the respiratory chain, we have a very specific method available to measure oxygen-dependent metabolism,' Paech explains.

The Warburg effect

In the course of their technological development work, Paech and his colleagues initially tested the method on three healthy subjects. As expected, images of their brains showed a high metabolic rate (oxygen consumption). They then examined ten subjects with brain tumours. In these patients, lactic acid accumulated in the tumour cells. This metabolic product is the result of the anaerobic metabolism which the cancer cells prefer – even when they have sufficient oxygen available. This phenomenon is known as the Warburg effect.

'With the help of oxygen x-nuclei imaging, we could show that the specific metabolism of the tumour can also be visualised in low-grade tumours, i.e. the tumour then shows as a region where no or hardly any oxygen is processed,' Paech explains. To achieve a reasonable signal and good contrast, the researchers at the DKFZ developed specific coils for the 7-Tesla MRI which can currently only be used for MRI scans of the head.

Comparability

Normal magnetic resonance imaging is primarily structural – it visualises water in the body. Visualisation of tumour growth through changed structures and destroyed tissue is only a secondary effect. 'The interesting feature of oxygen-17 imaging is that looking at the metabolic activity in the tissue takes things to a new level: It provides in vivo information about the tissue which should be viewed as complementary to the structural imaging techniques,' the expert explains.

Therefore, the researchers have not only gained new findings on the biology of brain tumours but also developed a new procedure that could help to characterise tumours more precisely, based on their particular metabolism. The researchers also expect that oxygen-MRI will provide valuable information for other diseases which go hand in hand with changes to metabolic processes such as Alzheimer's disease or multiple sclerosis.

The only procedure currently directly comparable with $^{17}O_2$ MRI is oxygen-15-PET imaging. However, $^{15}O_2$ is radioactive and decays with a half-life of about two minutes. 'We would require a facility for the production of $^{15}O_2$ right next to the hospital so that the isotope can be given to the patient within the shortest possible time. This is not practical in daily clinical routine,' says Paech, in explaining why $^{15}O_2$-PET imaging has not become established.

Apart from hydrogen, there are further x-nuclei which could be of interest for medical imaging. However, as yet there are no clinical or scientifically relevant studies for potassium, chloride- or magnesium nuclei. Researchers have made some progress with natrium imaging which measures the natural distribution of natrium in the body. 'Tumorous diseases result in changes to natrium signals as cell death,' Paech reports, 'and the development of oedema result in increased local natrium concentration.'

Daniel Paech MD. Dipl. Phys. (2011) completed his medical studies in 2015 at the universities of Karlsruhe and Heidelberg and at the Sorbonne in Paris. He now heads the 7-Tesla MRI in Prof. Heinz-Peter Schlemmer's department (E010 radiologist) at the German Cancer Research Centre in Heidelberg.

Sahlgrenska University Hospital and Medtron AG

Creating a refined contrast media

Shortly after the hospital opened the new hybrid operating room the SUH planned and built an extension specifically for the most advanced imaging facilities. The centre has theatres for both surgery with advanced imaging equipment and guided catheter-based interventional procedures, including cardiovascular and neurological as well as other organ and tumour treatment areas. The building houses nuclear medicine with gamma and PET cameras as well as diagnostic capability with radiography, computed tomography, ultrasound and magnetic resonance imaging.

It counts two neuro labs, three hybrid labs and four peripheral labs, yielding nine labs altogether in the two Interventional suites as well as a hybrid operating theatre with three hybrid ORs.

In the interventional department and in the hybrid operating theatre, the radiography department nurses work together with the operating nurses in shared facilities.

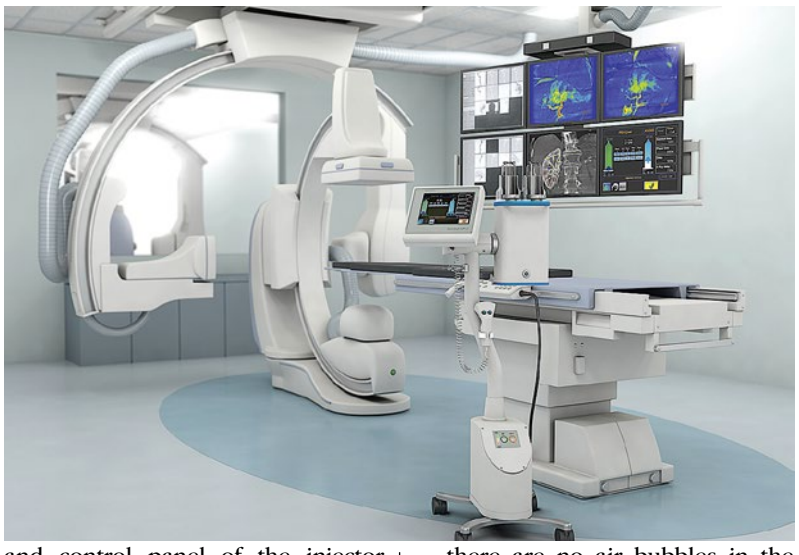
Medtron AG is a leading manufacturer of contrast media injectors, which has made its name on the international market: Across the globe, many thousand hospitals and diagnostic centres place their trust in the firm's contrast media injectors made in Germany.

Medtron's dual head angiographic injectors Accutron HP-D are frequently used in both the hybrid operating theatre and the neuroradiology department. The neuroradiologists alone operate three Accutron HP-D injectors and perform four to six interventions daily. The injectors are used for digital subtraction angiography (DSA), 3-D angiography and VasoCT.

Clear user requirements drove the redesign

A team of Sahlgrenska's radiologists, biomedical engineers and specialised nurses have been involved in the second evolution of the Accutron HP-D injector. Sahlgrenska has very experienced professional staff that was able to determine needs and technical features they were really looking for.

Roya Razzazian, radiography nurse at Sahlgrenska, explains which benefits she wanted to achieve: 'Clear view of the injection unit and control panel of the injector is important, and complete access around the table is critical.'



Roya's conclusion on the results after the redesign of Accutron HP-D are very positive: 'We are satisfied with the new Accutron HP-D. The injector serves us well.'

These top features were most requested by Sahlgrenska's experts:

- With the injection unit that is now 10 cm higher than before we have clear vision of the syringes at all times. Thus, we can ensure there are no air bubbles in the syringes.
- With the control panel that is now 15 cm higher than before, we can see the on/off-button and the screen at all times. Thus, we can control if the injector is working and see the current status of the injection.
- With the control panel that can now be swivelled by 180 degrees, we can operate it from both sides of the operating table. Thus, we can work alone or in a team.
- The wireless and mobile injector can be moved to and from the table quickly and easily. Thus, the injector fits easily into the crowded space around the operating table. There are no cables that could hinder us in any way.'

Technologically demanding and committed to cooperation

Magnus Eriksson, a biomedical engineer at Sahlgrenska, has an explanation for the success of the joint development project: 'We are innovators who push manufacturers to deliver better med tech. Also, we are cooperative and involve the whole team'.

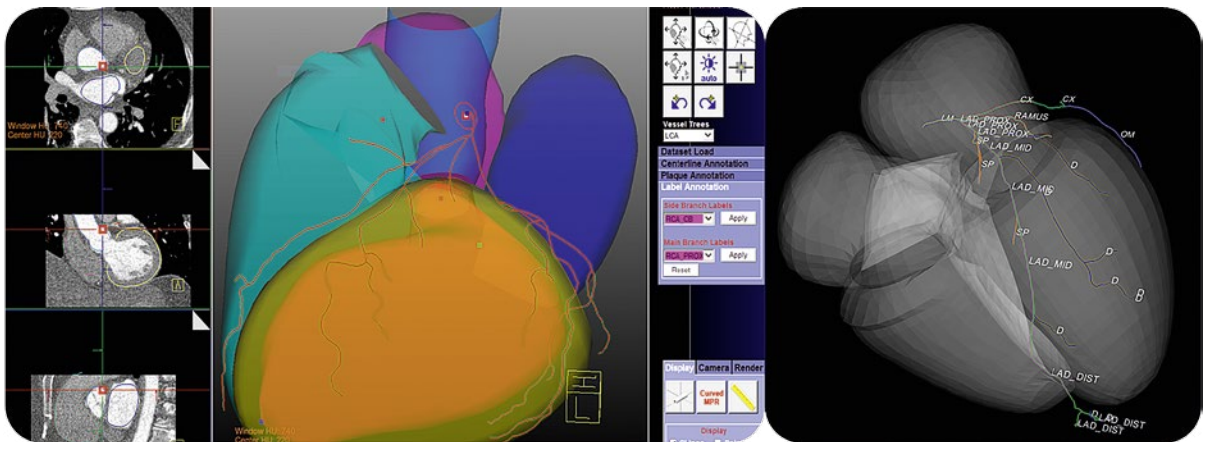
The double head injector brings additional benefits to Gothenburg, as it enables dilution of contrast media with the help of saline. This is important in a hybrid operating theatre, which provides cutting edge equipment for various radiology procedures and in neuroradiology, e.g. when contrast is injected through microcatheters to perform 3-D imaging of the complex brain vasculature.

In DSA, Accutron HP-D is connected to the catheter when the

The ascent of computerisation in radiology

AI for thorax-CT

As a highly innovative medical specialisation, radiology increasingly takes advantage of the possibilities offered by artificial intelligence (AI). Yet, there is no risk for the future of the specialty. Demands on this discipline are too complex, too communicative. Thus, machines will not replace a radiologist any time soon – of that Uwe Joseph Schöpf, professor of radiology, cardiology and paediatrics, and director of the Cardiovascular Imaging department at the Medical University of South Carolina (USA), is convinced. Using a few impressive examples, he explains what AI has to offer the radiologists.



It is true that the popularity of radiology declined in recent years among young medical graduates in the USA. There was just too much worry about entering a specialty that might just be made obsolete by progress in artificial intelligence. Meanwhile the trend has reversed again, simply because that is not expected to happen. The reason? There are far too many indispensable interpersonal competencies needed for success in radiology: communication with a patient and referring physicians; interdisciplinary procedures and a holistic view of the patient's current situation – not just of a specific image pattern. 'These are capabilities that a computer still cannot assume, no matter how good it is,' Schöpf points out. 'For that we still need capable and well-educated specialists.'

AI undertakes the time-consuming work

For the professor, AI constitutes a highly potent capacity to seriously improve the diagnosis using a continuously perfected image evaluation. What does this really mean? First there is the enormous time-saving AI provides – above all for measurements in quantitative imaging. Thus, an appropriately trained computer can automatically and precisely generate the Agatson score for calcification of coronary arteries within seconds. The same measurement takes between 15 and 20 minutes for a radiology trainee or specialist depending on the degree of calcification.

Another example is the automatic measurement of mitral valve dimensions. 'This is difficult for the human observer, because it moves in a three-dimensional space; even four-dimensional if heartbeat is considered. The 2-D image on the workstation is not well-suited to this kind of precise measurement.' The computer recognises no such restrictions. It measures automatically, fast and probably also better.

Artificial intelligence recognises and classifies fine branching in the coronary vessels with a high degree of reliability.

Genuine value added

That is not all AI can do. It can enrich findings with additional results and thus enhance them. So-called opportunistic screening delivers important information which is not sought routinely but can decisively improve diagnosis. A good example is emphysema quantification. The computer recognises, on its own, whether or not there is a pulmonary emphysema and can even determine its extension simultaneously.

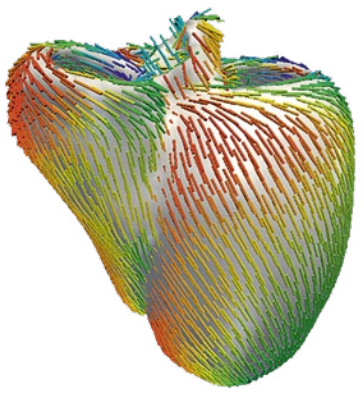
Without any further effort, this measurement is taken automatically and precisely with every thoracic CT. The same applies to measuring bone density. Detailed information about bone substance can be highly relevant for diagnostic and therapeutic aspects. A human observer, concentrating on other thoracic structures, easily overlooks this irregularity.

The measurement of the thoracic aorta to find an aortic aneurysm is a third example. Due to numerous curves in the course of the aorta, measurement is difficult for radiologists – but no problem for the computer; here it also measures quickly and accurately.

Two birds with one stone

'On one hand, we are currently working on the discovery of pulmonary nodules and, on the other, the automatic detection of coronary vessels and plaques.' Here, the long-term objective is to identify as many potential problem areas as possible with one and the same CT image. That means, with a lung CT, calcification of coronary vessels are automatically measured in parallel and, with a heart CT, there is simultaneous detection of pulmonary nodes. 'A very efficient procedure, impossible without AI,' Schöpf observes. 'We also work with AI especially in cardiovascular diagnosis to assess how serious a coronary stenosis is.' The focus here is measurement of the flow reserve. Results to date indicate that this examination could become part of clinical routine very soon.

In one fell swoop



The digital twin of a human heart contains information from imaging, the medical file and other sources and permits simulation and prediction of the effect of influences and therapies

Professor Uwe J Schöpf studied medicine in Munich and specialist training at the Institute for Clinical Radiology of the Ludwig-Maximilian-University. In 2001, with a keen interest in cardio-thoracic imaging, he left Bavaria for the USA where, he was to become a radiologist at the Brigham & Women's Hospital, Massachusetts, until 2004, Today he is professor of radiology, cardiology and paediatrics and directs the cardiovascular imaging department at the Medical University of South Carolina in Charleston.

The use of AI is very promising – even beyond image identification. Catchwords: structured reporting. Based on unstructured findings dictated by a physician, AI allows filtering of the relevant text elements and their transfer to a structured diagnosis. The advantage is obvious: more objective diagnosis, easier billing, better use in studies and also easier to understand for a referring physician. 'I see the value of structured diagnosis, but,' Schöpf points out, 'also the problem of practical implementation. The preparation of a structured diagnosis takes longer than one freely dictated. The physician has to click laboriously through web pages, in which all possible structures are queried, even the unobtrusive ones.' From his experience, he sees it as not particularly user-friendly for routine radiological operations. Hence the very promising use of the computer is even more welcome here. Moreover, the procedure can be applied to all organ fields, once the computer has been appropriately trained.

injector

radiologists and vascular surgeons are running imaging series or performing a 3-D angiographic procedure.

An advantage for the patient is the possibility of direct intervention in the case of narrowing or aneurysmatic vascular changes and bleeding. For example, if it turns out during the imaging that there is a constriction that can be treated with a catheter procedure, the therapy can take place in the same session.

Most importantly, by improving the procedures in the above described way, the new Accutron HP-D offers enhanced safety for the patients. It can help to reduce the contrast dose impact on the patient without affecting image quality.

A most reliable device

Reliability is important in Sahlgrenska's busy imaging and intervention centre. Magnus confirms: 'The Accutron HP-D is a very reliable device that always works. We don't have any issues or problems with it. It just works.'

A more complex question than 'good' vs 'bad'

Cystic pancreatic lesions

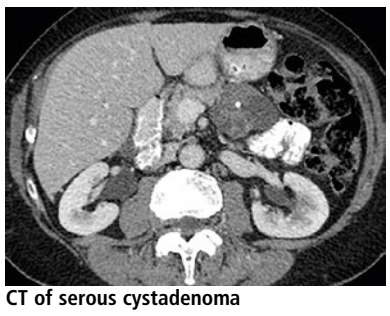
Cystic lesions of the pancreas can occur in many forms, not all of which pose a serious threat to the patient. A thorough diagnosis using multi-modality imaging is therefore indispensable to differentiate between benign and malignant lesions. We spoke with Professor Valérie Vilgrain, from Hôpital Beaujon, Hôpitaux Paris-Nord Val de Seine, in Clichy, France, about the prevalence of cystic pancreatic lesions and the right imaging tools to establish a reliable diagnosis.

'Pancreatic cystic lesions are very heterogeneous and extremely common,' observed abdominal imaging specialist Professor Valérie Vilgrain. 'Interestingly, their recorded prevalence is directly related to the imaging modality used for their detection. While prevalence on CT-scan is 2-3%, on MR it ranges between 13-45%. This is an especially important finding because, more often than not, the MRI would have been prescribed to examine an unrelated organ.

'As the number of MRIs performed increases, more pancreatic lesions are likely to be discovered. This makes our ability to differentiate between different lesion types – those with benign behaviour from the clearly malignant – of the utmost importance to diagnosis, treat and manage our patients.

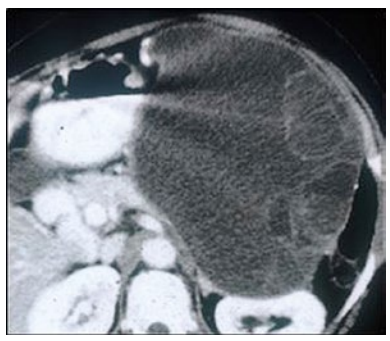
'In a patient with suspected pancreatic lesions, the general imaging work-up starts with diffuse abdominal ultrasound, then a CT-scan to assess the whole pancreas. It's important to ascertain that the pancreas is normal in its morphology and in its relation to the rest of the gastro-intestinal organs. CT is also useful for finding evidence of calcification.

'Further assessment of the pancreatic ducts, biliary system and surrounding parenchyma is then performed using MRI where higher contrast resolution facilitates imaging of the important relationship between the cystic lesion and the pancreatic ducts.'

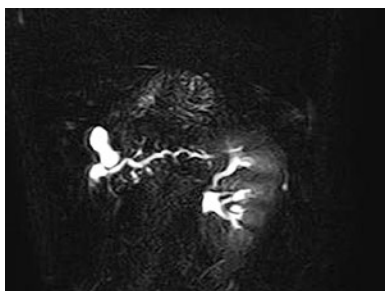


CT of serous cystadenoma

MRI of serous cystadenoma



CT of mucinous cystadenoma



MRCP of IPMN

Types of pancreatic lesions and differentiation

'The majority of pancreatic cystic lesions will be pseudocysts, which express benign behaviour and often result from acute inflammation of the pancreas (pancreatitis), and/or surrounding tissues. Of greater concern are neoplastic cysts.

'The three most important pancreatic tumour types are intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN) and serous cystic neoplasm (SCN). Again, the whole pancreas, especially the ductal system and its relationship with the lesion, has to be taken into account in identifying these lesions and imaging by either CT or MR is important to determine this.

'By their nature, IPMN is a tumour that can occur within the cells of the pancreatic duct. IPMN tumours often produce mucus. Although IPMNs are benign tumours, they can progress to pancreatic cancer. Here, imaging is of great assistance in the asymptomatic patient for deciding whether resection should be performed or not. If the lesion is in a side branch of the main duct and there are no other signs of malignancy, then observation for life, with regular follow-up is a viable option for management.

Advances in understanding

'If there is no ductal communication, the lesions are likely to be either MCN or SCN. The former group, generally solitary cysts, was once always treated by resection. However, advances in our understanding have enabled us to conclude that only a subset of these tumours are malignant or premalignant and, for the main part, when patient demographics, symptoms and other clinical findings are considered, these lesions can be managed with frequent follow-up, rather than surgery.

SCN can be considered as purely benign and, unless they become greatly enlarged and cause pain by compression, do not require resection.'

Are both genders equally affected?

'There is a clear gender distinction for the type of pancreatic cystic lesion found. IPMN is most frequently diagnosed in men, particularly middle-aged men, whereas mucinous and serous cysts are more common in women. Only MCN have clearly been defined by the presence of ovarian stroma at a rate of approximately 9:1. In the other lesion types, the reason for the clear gender differences that exist is not yet understood.'

Challenges to diagnosis of these lesions

'Accurate diagnosis is essential for correct patient management. Therefore, it's particularly challenging to get it right. For a good diagnostic work-up we need to consider the whole picture in front of us and not rely on just one technique or result. Patient, age, family history, sex, clinical background and co-morbidities etc. are all of importance in the diagnostic procedure and when considering management options.

'Histology is not a reliable option in cystic lesion differentiation but the imaging modalities of CT and MR are essential, and complementary, in identifying the nature of the lesion, position, size, calcification, nodule, wall thickness and, of course, its relationship with the pancreatic ducts.

'Endoscopic ultrasound, performed under general anaesthetic, is a more invasive technique and generally not performed early in the patient journey. Biochemical analysis of the cystic fluid is of highest utility to differentiate between mucinous and non-mucinous lesions, but is unable to distinguish between invasive and non-invasive MCN. We are now fortunate to have some accurate biomarkers, such as CEA, CA 19-9, CA 72-4, which form a panel of highly specific markers.'

Aim for the 2020 CT conference

'My main message is the importance of correctly integrating imaging into the diagnosis of these lesions. That CT and MRI are truly complementary techniques that both have an important place within a wider clinical picture, as clearly defined in recent European Clinical Guidelines for the successful identification and management of pancreatic cystic lesions.'

Professor Valérie Vilgrain is an expert in abdominal imaging specialising in liver, biliary and pancreatic diseases at Hôpital Beaujon, Hôpitaux Paris-Nord Val de Seine in Clichy, France. Her main research lie in diagnostic and interventional imaging of the liver, pancreas and bile ducts, with a particular interest in multidetector CT and MRI. She also directs The European School of radiology and is a member of several national and international societies, e.g. the Radiological Society of North America, European Society of Radiology, European Society of Gastrointestinal and Abdominal Radiology, European Association for the Study of Liver and the French Radiological Society. Among other involvements, she has been principal investigator of several large multicentre clinical trials and is currently on the Editorial Board of the Journal of Hepatology and Abdominal Radiology.

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