VOL 28 ISSUE 5/19 • October/November 2019

EUROPEAN HOSPITAL

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

See our ad on page 5

More competition among health insurers or among hospitals?

Temperatures rose significantly when a press release arrived at the Bundeskartellamt, Germany's competition authority. 'Does the Bundeskartellamt obstruct useful structural adjustments in the hospital sector?' the release asked. Issued by the organisers of the European Health Congress, it claimed that the authority had blocked 40 hospital mergers. In view of a recent study by the Bertelsmann Foundation, which urged that 50 percent of German hospitals be shut down, the claim sounded even more alarming.

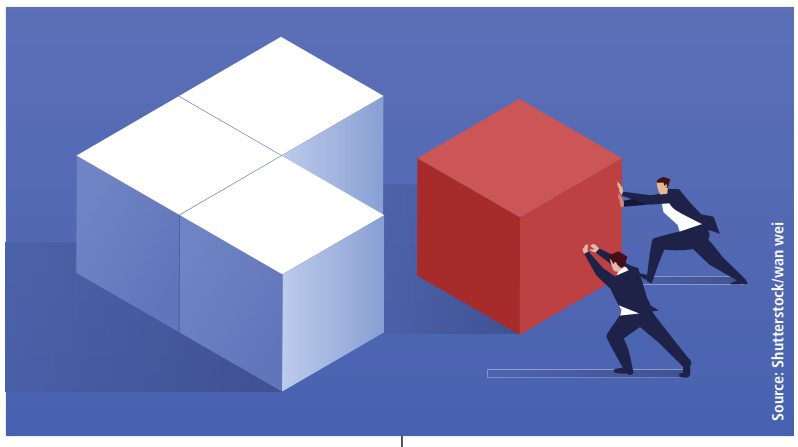
Report: Sonja Buske

'We don't know how this figure came about', said Andreas Mundt, President of the Bundeskartellamt. 'Of the 309 transactions examined between 2003 and September 2019, only seven were prohibited. This translates into 2.3 percent. How could such a low percentage of blockings undermine useful structural adjustments?'

Parts of the study are misleading

Mundt takes issue with the Bertelsmann study because, he said, it uses a different data pool than the Bundeskartellamt: 'It looks only at the location of the hospitals, not at the hospital operators. We, however, look at the operators, because they are the ones competing with each other, not the sites.' Case in point: the city of Cologne. 'According to the study, in the northern area of the city only one of the currently four hospitals is needed,' Mundt pointed out. 'But, if you look at the operators you notice that all four hospital sites are being operated by the same organisation. Thus, the Bertelsmann study is looking at the situation from a very different perspective than the one we consider important from a competition point of view. For our purposes the Bertelsmann study is in parts irrelevant. I am quite confident that the operators know best which sites need to be consolidated in order to be commercially successful.'

Any hospital merger decision by the Bundeskartellamt is based on a number of factors, most importantly the patients who will be affected by the merger. To determine this, the competition authority analyses the post codes of the patients who were treated in the hospitals under assessment. Mundt's team then asks which of those hospitals, from the patients' point of view, could be replaced and which hospitals compete on the regional level. If, post-merger, the patients will not have access to a hospital by a different operator, the merger is considered problematic.



Source: Shutterstock/wan wei

'We continue to be convinced that competition is an important aspect of quality assurance in the hospital sector,' Mundt elaborated. 'Competition forces the hospitals to offer ever higher quality services to attract patients. This is a 100 percent positive development.'

The Bundeskartellamt President added that mergers which are considered problematic in terms of competition might be allowed, as long as they fulfil certain conditions. He pointed out that there are other options to realise structural adjustments in the hospital sector, such as cooperation. For example, hospitals could create efficiencies by shared use of major medical technology, while maintaining diversity. 'Hospitals can share MRI scanners and thus save a lot of money,' Mundt suggested. When hospital mergers are problematic in terms of competition, or when hospitals fail to merge for other reasons, cooperation might be a useful alternative.'

'No new competition laws are needed'

This September, at the European Health Congress in Munich, Professor Achim Wambach, President of the ZEW, Leibniz Centre for European Economic Research and Chairman of the Monopolies Commission, asked whether new competition rules are needed for statutory health insurers. The Bundeskartellamt's answer in a nutshell: No. 'We have ongoing and intensive communication with hospital owners and can thus develop reliable best practices to safeguard competition. I don't have the impression that we miss cases that would need assessment. Moreover, we don't work in a static manner; we develop continuously. Today, for example, we also survey office-based physicians as to the basis on which they refer their patients to hospitals and we closely scrutinise quality measures hospitals take. The law is very useful and easy to implement.'

Wambach agrees by and large, however, he does see certain weaknesses in the implementation: 'Hospitals compete on quality – which can be improved by sheer size. This is something the Bundeskartellamt should consider in their assessments, rather than blocking mergers on principle only because two regional competitors are involved.'

More importantly, Wambach demands reforms in health insurers' competition. 'On the regional level, health insurers are often very powerful actors that wield influence – not always to the benefit of the patient. In this regard, the competition rules are unfair. The most important issue is: who protects the insured? It ought to be the insurers, but they lack the mechanisms, or they don't use them.' Thus, he demands that health insurers offer all services on an optional basis rather than current practice, in which the insured, i.e. customers, receive a standard package and can select optional coverage.

Quality agreements with hospitals

Additionally, Wambach suggests that insurers conclude quality agreements with hospitals. Patients receive optional treatments only in those hospitals that have an agreement. Patients wishing to exercise their free choice of hospital can do that but must pay a premium if they opt for a hospital that has no quality agreement. This structure, according to Wambach, would control patient flow and ensure quality. Moreover, hospitals would recognise whether their business model is appropriate or not. The forces of competition would come into play and the issue of hospital shutdown, as discussed in the study of the Bertelsmann Foundation, would take care of itself since the free market decides. Albeit 'that's a long way ahead,' Wambach conceded.

As Chairman of the Monopolies Commission, he would like to see politics have more confidence in the forces of competition among the health insurers: 'Currently, competition exists only on the price level. Why does the German Federal Insurance Office have to intervene any time an insurance policy is not commercially successful? We should give the insurers more free rein and let them test more. Consequently, not all insurers will be on the same level – but all will become more productive and more innovative – to the benefit of the patient.'

© Anna Logue Fotografie

In 2014, **Professor Achim Wambach PhD** was appointed to the Monopolies Commission, which he chaired since 2016. In that year he also became President of ZEW – Leibniz Centre for European Economic Research. He has served on the Scientific Advisory Board for the Further Development of the Risk Structure Compensation Scheme of the German Federal Insurance Office – the Bundesversicherungsamt (2017-2018). The professor also co-authored the expert opinion on the effects of a morbidity-oriented risk structure compensation scheme, as well as the expert opinion on the regional distribution effects of the risk structure compensation scheme.

Lawyer **Andreas Mundt** is President of the Bundeskartellamt (German Competition Authority) in Bonn since 2009. In 2010, he became a member of the Bureau of the OECD Competition Committee and, in 2013, head of the Steering Group of the International Competition Network (ICN).

www.healthcare-in-europe.com

Transforming healthcare

Necessary change – or destruction?

Dr Clemens Martin Auer is the special commissioner for health in the Austrian Federal Ministry for Health and Social Affairs, as well as president of the European Health Forum Gastein. The high-ranking Austrian civil servant performed a central function in all essential stages of healthcare reform in his country. This also included the introduction of the electronic health file (ELGA) in Austria. Auer, who studied philosophy and political science in Vienna, was most recently co-chair of the eHealth Network, the responsible agency head within the EU and, as coordinator of the EU eHealth Governance Initiative, responsible for the strategic orientation of the common eHealth policy of the Member States.

Report: Michael Krassnitzer

Dr Clemens Martin Auer knows 'disruption is an ambivalent concept'. Auer is president of the European Health Forum Gastein (EHFG), in which healthcare policy is discussed annually from a European perspective: 'For some, disruption is the promise of necessary change whilst for others it means suspicions and fears.' The term – a synonym for 'transformation' but also for 'destruction' – was the central topic of this year's conference titled: 'A healthy dose of disruption? Transformative change for health and societal well-being'. Auer comes to the point when he asks: 'How do we find the right measure of transruption in the healthcare sector?'

One of the great disruptors in healthcare is without a doubt digitisation. 'The digital transformation offers the opportunity no longer only to react to disease but rather for us to increasingly dedicate ourselves to proactive and preventive treatments,' stresses Professor Ran Balicer, founding director of the Clalit Research Institute (Israel). However, it also brings with it great changes: 'If we look at the digital transformation, the key word is not "digital" but "transformation", Balicer emphasises. 'It makes no sense to promote digitisation of healthcare without first effectively revolutionising the fundamental care processes. In other words: if you digitise a defective clinical process, then you get an expensive defective digitised process.'

The EU invests in AI

The EU invests in and supports the development of the 'digital transformation' often cited at the EHFG 2019. The European Commission is currently working on a strategy to support artificial intelligence (AI) at EU level that also includes the use of AI in healthcare, as Marco Marsella, head of the General Direction Communications Networks, Content, and Technologies (DG CONNECT) explains: 'The digital transformation will be data driven.' So, at one conference session one could learn how the European Centre for Disease Control (ECDC) uses 'big data' for surveillance of nosocomial infections, or who the World Health Organisation (WHO) localises disease outbreaks in the context of EIOS (Epidemic Intelligence from Open Sources) based on indicators in the media – both classical and social formats.

Of course, EHFG 2019 also tries not to forget the human side, the 'human touch' in the digital transformation. 'If these new technologies are implemented, attention must be given not to marginalise parts of the population,' warns Dr Indra Joshi, who, as Digital Health & AI Clinical Lead in the British National Health Service (NHS), is responsible for the introduction of an app that enables access to a series of services. This is especially important in the case of vulnerable population groups, such as the aged who feel insecure with modern technologies, or migrants who might not speak the local language: 'They must be able to choose whether they want to care for their treatment digitally, or prefer to consult a physician personally.'

There is a second key word in the conference title: 'well-being' – an allusion to Finland's presidency of the European Council. The Scandinavian country has placed well-being – and hence a health issue in the widest sense – high up on its agenda while currently presiding over the EU Council. 'People who feel well are less frequently ill, work, are innovative and pay taxes,' Dr Paivi Sillanaukee, General Director of the Finnish Ministry for Social Affairs and Health, explains:

'In aging populations well-being has a countervailing effect also for the rise in costs of social services and healthcare.' The demand for equal status, improved employment options for women, as well as the compatibility of professional and private life, are central objectives of the 'Economy of well-being' propagated by Finland.

The European Semester

'The instrument for implementing our program is the 'European Semester', explained Sillanaukee. This is a budgetary instrument that permits the EU to perform an early review of national budget and reform bills before these are adopted by the national parliaments. Every year in May, the European Commission publishes proposals on this basis as to what it feels each individual country could do better. Funds are tied to these 'recommendations'. So, if a country does not fulfil the demands, then it loses money. The high-ranking Finnish civil servant is convinced that 'the legitimacy of the Union among the citizenry is strengthened if well-being is given a clear priority among the EU's long-term objectives.'

Drug-eluting stents reduce risk of lesion failure

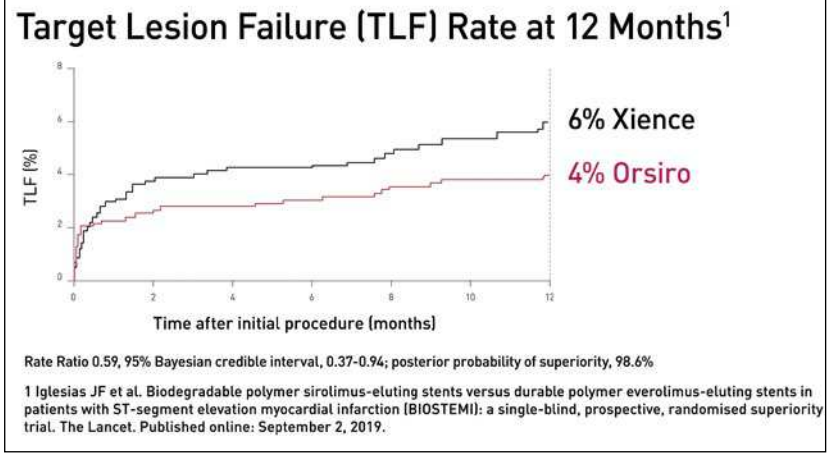
Orsiro DES demonstrates superiority in STEMI patients

Dr Juan F. Iglesias from Geneva University Hospitals, Switzerland, unveiled results of the BIOSTEMI trial at the latest ESC Congress in Paris.

About 30 percent of patients undergoing primary percutaneous coronary intervention (PCI) suffer ST-Elevation Myocardial Infarction (STEMI) – the most acute form of coronary artery disease.

Caused by a complete thrombotic occlusion, it is associated with significant morbidity and mortality.
Following his presentation at a Late-Breaking session at the European Society of Cardiology Congress,
Dr Juan F. Iglesias, from Geneva University Hospitals, has communicated the benefits of the Biotronik Orsiro drug-eluting stent (DES) for that challenging STEMI patient group.

Iglesias is a co-principal investigator of the BIOSTEMI clinical trial, which found using Orsiro to be associated with a 41 percent lower risk of target lesion failure (TLF) at 12 months, when compared to Abbott's Xience. The study enrolled 1,300 patients and has since been published in The Lancet (Lancet online: Sept. 2019. https://doi.org/10.1016/S0140-6736(19)31877-X).



Although STEMI patients make up a third of primary PCI cases, BIOSTEMI is the first randomised clinical trial, powered for superiority, to look at them specifically.
'BIOSTEMI is not only the first randomised clinical trial to compare two contemporary drug-eluting stents, it's also the first randomised clinical trial comparing two new devices with high standing platforms in patients with STEMI,' Iglesias says, adding that he hopes the trial will lead to further research gaps being closed.

'The use of these stents is mainly supported by non-inferiority trials, including all-comer patients, and for the first time we have a sub-group of patients that's been shown to benefit from a dedicated stent.'

The ultrathin Orsiro was launched in the CE market in 2011 and received FDA approval in 2019. Orsiro's safety, efficacy and clinical performance has been investigated in an extensive clinical program with more than 48,500 patients enrolled so far.

'Based on the data, compared to the Xience stent, Orsiro is a superior solution for STEMI patients. In this patient group, vascular healing is a challenge due to the complex environment with the vessel,' Iglesias explained. 'With Orsiro, we can incrementally improve patients care path.'

Cross-border exchange of patient data

A digital transformation is happening

In 2011, Maltese pharmacist **Martin Seychell BSc** became EU Deputy Director-General for Health and Food Safety (DG SANTE, formerly DG Health and Consumers (SANCO), as the directorate was known until 2015). Before becoming an EU official, he was the Director of Environment Protection at the Malta Environment and Planning Authority.

Report: Michael Krassnitzer

'Compared to other sectors, healthcare is lagging behind in the systematic use of electronic data,' says Martin Seychell, EU Deputy Director-General for Health and Food Safety (DG SANTE) and top official at the European Health Forum Gastein (EHFG). 'However,' he adds, 'this is changing and the digital transformation is happening right now.'

The EU Commission has recently made a series of recommendations on the development of a European system to give citizens access to their electronic patient data across all member states. The objective is a European format that allows the safe exchange of electronic patient records under adherence to data protection regulations. 'Each year, more than two million EU citizens need to use health services when abroad,' Seychell explains. 'In these cases, electronic patient records (EPRs) can provide important information. EPRs not only make access to information easier but also improve the continuity and quality of medical treatment.'

Finland, Estonia and Croatia

Work is underway to develop the infrastructures to exchange healthcare data within the member states as well as at a European level, including the specifically designed eHealth Digital Service Infrastructure, eHDS. A number of member states already started a cross-border exchange of patient summaries and electronic prescriptions. Finland, Estonia and Croatia use the eHDS to exchange electronic prescriptions: Estonian and Croatian pharmacies can hand out medication to Finnish citizens, prescribed to them electronically by their GPs. 'Almost 5,000 electronic prescriptions were redeemed in the first few months,' Seychell says.

Patient summaries can be exchanged between the Czech Republic, Luxembourg and Croatia via eHDS. These are short versions of EPRs that provide doctors with essential information on patients. Luxembourg doctors now have digital access to patient summaries of travellers from the Czech Republic or Croatia. 'Malta and Portugal are soon to follow,' Seychell reveals.

22 countries by the year 2022

The plan is for 22 member states to be able to exchange EPRs by 2022. According to recommendations made by the EU Commission, the next step will be to extend the scheme to the exchange of laboratory examinations, hospital discharge letters, radiological imaging and the respective results. 'The objective is a complete electronic health record,' Seychell explains. He believes the basic prerequisites for this will be interoperability as well as data protection and safety.

An interchange format for electronic health records (European Electronic Health Records, EHR) is to be developed. The specifications for this interchange format are to be regularly monitored and updated to react to people's changing needs, as well as to technological developments. 'Safety and the protection of privacy are of essential importance for people's trust in electronic health records,' Seychell emphasises. Therefore, the exchange must be carried out in full compliance with the general data protection regulations that govern the framework for the protection of personal data. Furthermore, the EU Directive on the security of Network and Information Systems (NIS) sets out a number of safety measurements for network and information systems.

'All this will not happen without massive investment on national and EU levels,' the top EU official again emphasises. The EU Commission has already initiated a number of financial instruments. The 'eHealth Network' of the respective EU heads – under the leadership of Dr Clemens Martin Auer (as it so happens, president of the EHFG 2019) – has developed guidelines for such investments into the digital infrastructure. 'Whoever is looking for EU funding for investments into the cross-border exchange of healthcare data needs to adhere to these guidelines,' Seychell emphasises.

FDA expected to amend safety statements

Rebuttal: Paclitaxel-coated devices are safe

This January the US Food and Drug Administration (FDA) issued a safety alert about paclitaxel-coated stents and balloons for arterial revascularisation in the lower limbs, following findings from a meta-analysis of 28 randomised controlled trials that involved 4,663 patients. This suggested there might be a two-fold increased risk of death among recipients of these devices.

However, according to an 11-year study of nearly 65,000 patients, published in the European Heart Journal in October, these coated devices are safe and not linked to a mortality increase,

Since 2007, when paclitaxel coated stents and balloons were first used, up to 2015, the recipients continued to be monitored till 2017. The paper's first author, Dr Eva Freisinger, at the University Hospital Münster, Germany, said: 'Our findings show that paclitaxel-based devices are safe and are not associated with an increase of death. To our knowledge, this is the largest real-life group of patients that has been evaluated with long-term follow-up from the time that paclitaxel-coated devices were first introduced.

Our work provides a solid base of evidence that will be difficult to rebut. We expect the FDA and other regulatory authorities will very likely amend their statements on safety concerns on paclitaxel-based devices.

'Paclitaxel is an agent that prevents the proliferation of cells; it is used for coating stents (tubes) and balloons because it limits the growth of scar tissue and a recurrence of blockages in the treated arteries (restenosis). Drug-eluting stents and balloons have been used in millions of patients with lower extremity artery disease worldwide, with over 55,000 balloons and 6,600 drug-eluting stents implanted annually in Germany alone, of which 97% use paclitaxel. The concerns raised by the meta-analysis at the end of 2018 and the subsequent FDA letter of concern to healthcare providers, resulted in an estimated 50% drop in their use. In the current study, researchers in Germany retrieved data from 9.2 million people in the health insurance scheme, Barmer, to identify all who had a first endovascular revasclarisation for lower extremity artery disease between 2007 ad 2015. None of the patients had been treated previously with paclitaxel-coated devices because these were only introduced in 2007. However, during the follow-up period to 2017, many patients may have had more than one type of device fitted in subsequent procedures, which was taken into account by the researchers.

Transferring research into daily routine

AI possibilities and probabilities

Although some people foresee artificial intelligence easing medical workloads, many challenges arise before that dream can begin. Dr Felix Nensa and Dr Bram Stieltjes described such hurdles in an 'Artificial Intelligence in Medical Imaging' session held during a SITEM School Symposium in Bern, Switzerland.

Report: Daniela Zimmermann

Whilst artificial intelligence (AI) has potential, actually delivering that asset into routine medical practice remains a major challenge. Recently discussing 'Translational AI – from bits to bedside', radiologist Dr Felix Nensa, from Essen University Hospital in Germany, pointed to headlines that AI had helped to save lives, or that machines were supposedly better than radiologists. But, he noted, the tone of those headlines has been changing – indicating a peak in AI development. 'Now,' he said, 'to get to a plateau of productivity, we really need to be translational. We need AI to do something useful for us.'

The hype around AI results from several decades of continuous exponential growth in computer hardware, the power of computers, and storage, which brings with it a lot of data.

Is big data always big value?

However, Nensa added: 'You have to be careful not to equate big data with big value. Only if we have the ability to analyse this data does it turn into value. We are producing more information but lagging behind in our ability to analyse this data. The big hope is that AI, or methods of machine learning, will help us close this gap and extract more value from our data.'

Sharing examples from radiology, he said decades of information from images had simply gone into archives and nothing further had been done with that valuable data. However, radiomics – among new buzzwords in radiology – is seeing information extracted from tumours, in terms of their shape and texture, with machine learning applied to the data to create predictive models or future treatment plans.

A tumour's N- or M-stage, he said, may be predicted by looking at a primary tumour. Or, for brain tumours, where there is reluctance to carry out a biopsy, machine learning on PET-MRI data could be used to predict its mutational status. Yet, he still does not consider radiomics translational, because most methods need a manual tumour segmentation, and there are also issues of standardisation, validation, and clinical acceptance. 'Radiomics is interesting research-wise and we should go for it, but there is almost nothing I see in five to ten years in clinical routine,' Nensa said.

At the centre for liver transplantation in Essen, he said a tool has been created to automatically segment the whole liver and produce reports. He also outlined how machine learning can be used to predict how liver lobe will grow and predict future liver remnant in patients. A good machine learning model starts from a good question, he emphasised. 'If you identify a clinical problem find what really needs improvement and then understand the problem and specify data, you can communicate that with data scientists, who can design a system. After that, it's important to get these clinical models back to clinical routine early, to validate them.' While the first try-out will probably not work that well, the process is repeated with further iteration to deliver a tool good enough to work in clinical routine.

Nensa outlined the importance of medical informatics in translation and integrating tools into workflows. 'Medical informatics is needed to deploy AI tools into a hospital infrastructure because if it doesn't work in the clinical routine, it's worth nothing,' he added.

In bone analysis, for example, AI could be used to mimic a radiologist's workflow with stacked neural networks, harnessing the specialist's knowledge of workflows into the data science for tools to work better.

Is big data always big value?

However, Nensa stressed that he does not think AI could or would replace radiologists or radiology. 'Radiologists using these tools will get much more efficient much faster than those who reject them. In the end, radiologists who refuse to use these methods will be replaced – not by AI, but by other radiologists who do use these tools.'

On AI use theories recently discussed at major radiology conferences, as well as the point about radiologists already operating at near capacity and needing new technology to become more effective, he said: 'That's because we are getting more data every day and we cannot scale by just getting more efficient by ourselves, so we need tools to help us to scale and provide real-time diagnostic support.'

Rather than an autopilot, AI will be a co-pilot and leave radiologists to focus on vital tasks. It will not take jobs from radiologists, he confirmed, but will aid efficiency with routine tasks delegated to automation. 'In the end,' Nensa concluded, 'we'll have super-diagnostics, where all this information will come together and we, with the help of machines, will have oversight of all data, providing better and more sophisticated real-time diagnostics. This is key to personalised medicine.'

Challenges to AI projects

Dr Bram Stieltjes, from Basel University, outlined a range of challenges and hurdles involved in developing artificial intelligence projects in a clinical context.

As Head of the university's Research and Analysis Services Department, his presentation 'AI in a clinical context; get ready to make your hands dirty!', tempered expectations and focused on why AI in a medical context can be so difficult.

He warned that a 'huge over enthusiasm' is circulating around medical data on what can be done in the context of AI. A key issue with machine learning is having sufficient information and items in reports, in the first place, to be able to extract meaningful information. In a significant proportion of cases, Stieltjes feels reports are incomplete.

For structured reporting, he said, standard sentences must be a key element, but the aspect of 'probability' is often overlooked, and its lack is a limitation. 'Probability is the only way for us to know what you are thinking and the only way to use that data afterwards for a machine learning or AI project. If you do not add probability you are lost,' he observed. Adding probability brings an extra dimension to reports and could help in future learning and thinking. 'Recording medical thinking like this not only helps to train algorithms but also to train doctors in a really quantitative way.

'The whole structuring of medical data not only touches on training algorithms to replace what doctors do, but also trains doctors in a completely different way.'

There should also be a direct connection to the image. 'Today, what you have with AI projects is that you are really looking for a needle in a haystack at best and sometimes, in searching for a needle, you just find hay.'

Within a healthcare setting, he said, clinical data is saved for clinical documentation without much consideration of research. 'It's relatively easy to find all the data points from one patient, but even the databases that control our clinical applications are not built to find all similar patients, or all patients with the same exams.'

To create an effective machine learning application, he explained that auxiliary tools are needed that incorporate a risk element and technical descriptions. Stieltjes's team at Basel University reorganised their available data for research purposes and re-indexed technical exams in a re-think on the way they were dealing with data.

Using the search engine for as many patients as possible who fulfilled their criteria, they could investigate 12,000 MRI scans in 48 hours. 'It's a whole different way to work and enables interactive data interrogation and maybe drives the hospital infrastructure,' he said.

In a healthcare setting, he warned, there can be barriers to sharing data and acquiring it from other departments for an AI project, and also pointed to disappointments in the length of time it takes to develop an AI project. Moving radiology – and other fields – to structured text has intrinsic limitations, he said. Obtaining good data will still not solve all the problems, especially the connection between text and image.

However, in a scenario where all data created in a medical context is structured can help with modelling the data, and in making a virtual model of organs and predictions. 'I think this highly depends on how seriously we take the data-driven organisation of medicine,' Stieltjes said. 'We shouldn't organise ourselves around diseases, doctors and specialties; we should analyse what data elements are important for decision-making and how we get them.' The focus should be more on the data stream, rather than what is necessarily most convenient for the clinician, he said. 'If we can turn that thinking error around, I think we'll see rapid progress. If we don't, I think we'll talk like this for decades.'

Directly after completing his final school exams, **Felix Nensa** freelanced as a software developer for the Research Institute for the Diagnosis and Treatment of Early Lung Cancer at the Augusta Hospital in Bochum. At that time he also took a distance learning degree course in IT (2000). His medical studies, at Ruhr University in Bochum (2001-2007), included two semesters at the University of Strasbourg in France. In 2011, Nensa became a registrar at the Institute for Diagnostic and Interventional Radiology and Neuroradiology at Essen University Hospital. He manages research projects on PET/MR, Cardio-MRI and DCEMRI.

Bram Stieltjes MD PhD is VC of Research at the Department of Radiology of the University Hospital Basel and has recently formed a new department for research and analytical services in IT. In this role, he aims to integrate technical developments in physics and computer science into medical data science projects. His resident training is in radiology but he also had a year of training in child psychiatry and radiation oncology. He also headed a multidisciplinary group consisting of members from physics, medicine and informatics at the German Cancer Research Centre.

Impressive advances reported at Intelligent Health 2019

Notable medical AI in China

Report: Cornelia Wels-Maug

September: Basel, Switzerland: 'Intelligent Health 2019', a conference dedicated to artificial intelligence (AI) in medicine, underlined the growing interest by the rising number of attendees – 1,400 in 2018, its first year, to 2,027 this year.

With examples of AI use from around the world, the common thread throughout was how AI can serve humankind by enabling better understanding of patients and offering the means to improve productivity and effectiveness. It has the potential to render the dream of precision medicine a reality, according to one speaker proclaiming the potential benefits.

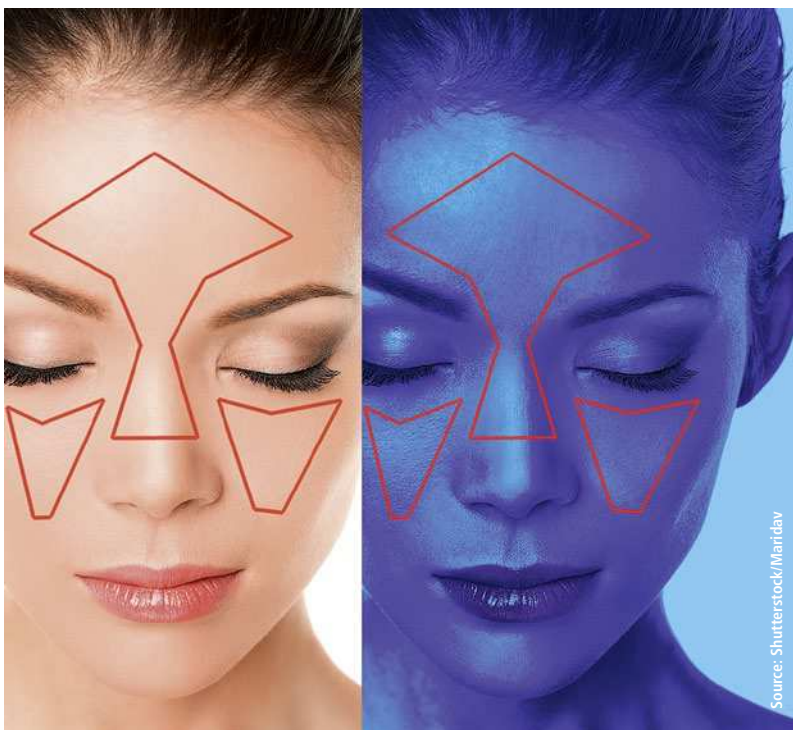
Sizable medical use of AI

The extent to which AI is already used varies substantially between countries. The Xiangya Hospital, Central South University, Changsha, shows the largest medical use of AI and smart care in China, according to Professor Weihong Huang, who works in the hospital's Department of Dermatology, and for the Mobile Health Ministry of Education – China Mobile.

Founded in 1906, the 3,500-bed Xiangya Hospital has a catchment population of 100 million people and serves about three million outpatients and 130.000 in-patients annually. It belongs to a group of 44 comprehensive public hospitals in China that are directly administered by the Ministry of Health. What also sets this hospital apart is that it is 'the first and only ministry key laboratory in health information technology of China and specialises in mHealth, big data, AI and IoT', Huang explains. Based on its profound database of medical information, the hospital has been deploying several AI-use cases to determine the effectiveness of artificial intelligence.

AI-based decision support – on par with doctors

Given the extent of patient data collected over recent years, Xiangya Hospital oversees a substantial database of medical information that spans well over a decade in most cases: the compilation of medical orders (20 bn) and drug information (30 bn) has been going on for more than 15 years; lab results (+400 mil) and examinations (+250 mil) have been collected for more than 10 years; medical records (1.8 mil) for seven years and imaging reports for more than six years respectively. This trove of information has prompted the hospital to look at ways to use it for AI-based applications in an attempt to offer 'smart' services: 'We need new business that allows for more intelligent, accessible and affordable care', says Huang.



Patients can photograph their facial skin conditions and have them interpreted by an AI-based algorithm.

Skin care based on image recognition

In China, skin diseases are a widespread burden, with high rates of allergic skin reactions and significant mortality rates due to skin cancer. The dermatology department of Xiangya Hospital organises the largest national biological sample bank for rosacea, lupus and skin cancer, Huang explains. It also possesses China's largest clinical image dataset of skin diseases.

The image library is the key enabler for Xiangya's so-called smart care platform, which contains one million dermatopathology pictures, a standardised skin disease library with 400,000 images, and a tagged picture repository of 20,000 images respectively.

Based on those images, the dermatology department created a dataset containing 2,656 facial images showing six common skin diseases (seborrheic keratosis, actinic keratosis, rosacea, lupus erythematosus, basal cell carcinoma and squamous cell carcinoma) and tested the ability of convolutional neural networks to diagnose those six skin diseases accurately.

At a later stage, patients were asked to photograph their facial skin conditions with a mobile device. Subsequently, these were interpreted by an AI-based algorithm. 'The results are comparable with those from dermatologists', Huang says. In the case of psoriasis, he explains, the algorithm even performed slightly better than a group of 25 dermatologists when interpreting a sample of 100 images.

There is an insufficient number of dermatologists in the region so, backed by these findings, in November 2018 Xiangya Hospital resorted to launch the first dermatology Internet hospital licensed to operate online in China. Furthermore, Xiangya is collaborating with over 100 other hospitals across 30 provinces and has established the first national skin cancer collaborative network to enable a faster access to diagnosis and subsequent treatment for patients.

More AI-supported services

Xiangya Hospital also deploys AI for other cases to make better use of limited resources via automation. This includes an interactive app that enables patients to upload their medical history, including pictures, ahead of an appointment, to free up time for the actual diagnosis when visiting a clinician. Another example is the so-called 'smart cervical cancer screening' programme, which assists in examining 60 million women annually by reducing the time it takes to evaluate the involved pap test slices. 'We want to bring down the time for evaluation of the slides from currently 60 seconds to 50 and even 45 seconds', Huang explains. 'Currently, we review 200 slices per day; this programme will help us to increase this to 300 slices per day in the future.'

Health IoT – the future

Huang is convinced that the future of healthcare will be data-based. Hence, he stresses the importance of IoT for generating a broader data base of medical information and outlines his vision of health IoT. 'H.IoT will be the new thing. We want to use health data more effectively to enable smarter care. For this, we need to establish a consistent management and quality control of health-related data from inside and outside the hospital. We even need to collect data that is small, dirty and incomplete', Huang postulates. 'Data is good. The future will be a smart home', he confirms, urging his audience: 'Don't be lazy'.

Weihong Huang holds a B.Eng. degree in automation, an M.Eng. degree in pattern recognition & smart control from Southeast University and a Ph.D. in computer science from Nanjing University, China. He was a Postdoctoral Research Fellow with CNRS University Lyon 1 in France, a lecturer in the Department of Computer Science, University of Hull, UK, and a Senior Lecturer at the School of Computer and Information Systems, Kingston University, UK. In 2016, he became a professor and Depute Director of the Mobile Health Ministry of Education-China Mobile Joint Laboratory, Xiangya Hospital, Central South University. His research includes mobile health, AI in healthcare, cognitive computing for healthcare, semantic multimedia computing, and knowledge graph applications. Huang is a Committee Member of the China Hospital Information Management Association, a Standing Committee Member of the Medical and Health Big Data Evaluation and Assurance Board of the Chinese Health Information and Big Data Association.

The first dermatology Internet hospital in China using AI for improved diagnosis.

Specialist lab physician

Lab services: Don't c

In recent years, whenever the German media reported on laboratory medicine, questions consistently arose: 'How can excessive costs for lab services be cut?' and 'How could money saved be distributed among other medical specialists and general medicine practitioners (GPs)?'

The questions are myopic in their failure to address two important aspects of laboratory medicine – its significance for patient well-being and the preconditions that should be fulfilled to operate a lab successfully. These are closely intertwined, since lab medicine drives and is driven by innovation and thus requires ongoing and high capital investments. Without those investments medical progress cannot arrive. There is a third neglected aspect: innovative tests – even if expensive – might well reduce overall healthcare costs.

Chemist and physician **Dr Andreas Bobrowski** chairs the Association of German Laboratory Physicians, and promotes the rational handling of lab diagnostics by developing and implementing diagnostic pathways in healthcare. Early in his career, he joined a Lübeck-based laboratory group of which, 12 years later he became head (2005). A delegate to the regional Association of Statutory Health Insurance Physicians Schleswig-Holstein since 1999, he has been the only lab physician delegate in the National Association of Statutory Health Insurance Physicians since 2011.

66% of medical diagnoses are made by lab physicians*

Roughly 2.5 percent of healthcare costs reimbursed by German statutory health insurers are generated in the laboratory. No doubt this money could be spent more wisely if payers and politicians drew the right conclusions. Over recent years, lab medicine has developed from a care-relevant to a system-relevant cross-sectoral discipline, which greatly influences the direction of the healthcare system as a whole: two thirds of all diagnoses are made, or confirmed by, approximately 1,000 hospital-based and office-based lab physicians.

Specialist lab physicians, aware of their influence in healthcare, are drafting lab diagnostic pathways and guidelines for their discipline. Inspired by the USA initiated campaign 'Choosing wisely' – based on preparatory work in the German Society for Clinical Chemistry and Laboratory – the National Association of Statutory Health Insurance Physicians, along with the Association of German Laboratory, are developing ways to introduce those pathways and guidelines into medical practice.

Their recommendations explicitly aim to enable high quality and cost-efficient care, particularly when complex and expensive therapies are involved.

Teamwork is crucial

Close teamwork is necessary between referring GPs and hospital-based physicians on the one hand and lab physicians on the other. In this well-structured landscape of diagnostic and treatment pathways the 'four-eyes' principle (approval by at least two people) is the alpha and omega of patient safety, being a safeguard against wrong diagnoses and waste of resources.

However, benefits culled from this kind of cooperation depend, to a large extent, on the significance of lab physicians and the appreciation they receive. For instance, in the Netherlands cooperation with microbiology has contributed significantly to one of the lowest MRSA rates worldwide.

In Germany, Austria and Italy, lab services can be provided and assessed only by a lab physician, which creates a communication structure where the doctors involved are on equal footing, ensuring high diagnostic quality and treatment safety.

In countries where lab services are not necessarily provided by lab physicians, but by medical technicians, results are forwarded to the referrer without further assessment. Thus the referrers cannot discuss them with a lab physician who is well versed in all issues surrounding lab analytics.

Source: Berufsverband Deutscher Laborärzte

Andreas Bobrowski and colleague evaluate a SDS electrophoresis to differentiate proteinurias.

On the European level, healthcare systems remain very different, even in diagnostic-technical disciplines, although medical diagnostics manufacturers, as well as professional associations, have long pushed for Europe-wide standards. In several EU Member States, and Switzerland, clinical-chemical and haematology basic services are provided on site, while, in Northern European countries, Benelux, Germany and Austria, large service provider groups with large catchment areas have evolved.

These significant differences in services provision have created a wide variety of reimbursement structures within the EU. The number of tests have also increased and innovation pressure has intensified, while all healthcare systems record shrinking resources and increasing morbidity rates.

Which current system is therefore best-suited to overcome future challenges? In terms of sheer numbers, lab medicine in Germany is facing the biggest task because, with 18 visits per person per year, Germans spend far more time with their doc-

A peek in the medical lab: receipt and handling of test samples

Source: Berufsverband Deutscher Laborärzte

Designing lab automation and environments

Human/Computer Interaction cha

The key challenge of Human-Computer Interaction (HCI) in creating a productive and efficient future laboratory was examined in detail by Andreas Schuller from the Fraunhofer Institute for Industrial Engineering in Stuttgart, Germany, during the recent SLASEurope2019 conference in Barcelona, which drew in more than 1,000 scientists and technologists.

Andreas Schuller currently leads the Interaction Design and Technologies team at the Fraunhofer Institute for Industrial Engineering in Stuttgart. He studied Computer Science and Media at the University of Ulm and Interactive Systems (Programming) at Monash University in Melbourne. In research and industrial projects, his interest is on the connection of the human-centred design process with the technical development of innovative user interfaces. His research focuses on the development of new interaction possibilities for industry 4.0, the implementation of mobile networked applications and intelligent user interfaces as well as design patterns for security and privacy of users.

During his presentation, 'Workplaces of the Future: Future Topics and Trends for Human-Machine Interaction – Implications for Lab Automation', Schuller looked at three key areas that would impact on the laboratory of tomorrow. These are: the driving forces that shape how workplaces will look; relevant research themes his team is working on; and what the implications are for Lab automation.

'In a nutshell,' he said, 'it is essential to address HCI and interaction design for lab automation equipment and environments due to its increasing future importance and major upsides and benefits for companies.

Driving forces that will shape how workplaces will look in the future include: demographic and shortage of skilled workers; effects of globalisation and demand for more speed and flexibility from companies; cultural changes at the workplace try to find a better work-life balance; and advancements in digitisation and Artificial Intelligence (AI).

'Due to these factors,' Schuller added, 'it's increasingly important for interactions between workers and their instruments to take place in a frictionless manner. Workers need to grasp interfaces quickly. Additionally, the technical advancements must allow for closer collaboration between workers and smart systems, where the worker complements these systems by training them, and AI and machine learning allow for better assistance of employees than ever before.'

Focus on conception, design and development

Schuller heads the Interaction Design and Technologies team at the Fraunhofer Institute for Industrial Engineering, which develops strategies, business models and solutions for digital transformation. Their focus is on the conception, design and development of human-technology interaction, aiming to make the most of the opportunities offered by digitisation through novel forms of interaction.

Current research themes being developed by his team include adaption and personalisation of user interfaces; creating shared knowledge spaces between employees and AI systems; making digital information available on the spot (through augmented and virtual reality, such as in a medical setting); and quantifying physiological data.

'Sensors allow for a novel kind of context detection of the user,' he explained. 'Systems can automatically set themselves up to accommodate for different tasks within the work context, or different personalised input modalities for the user, also enabling accessibility features.

'In increasing collaboration environments between employees and smart systems, the aim is to foster common knowledge and information data set. The important question here is: how can we incentivise users to provide this kind of information?' By quantifying physiological data such as heart rate, brain activity and galvanic skin response, researchers can attempt to derive conclusions towards the emotional components in design, or identify cognitive dimensions such as awareness during a certain task.

However, he stressed that there are implications for lab automation. 'To create effective and innovative interactions that also work for the coming years, it's important to gain an understanding and overview of the technical options available,' he explained. 'We have created a taxonomy of interactions or interaction space that can serve as a kind of guideline. When it comes to evaluating technology fit, it is important to be aware of relevant standards that play a role for the context and task.

Employees must be involved in the process

'The second point is to methodically involve the employees or existing system users in the design process. Only they have the perspective and

Virtual Reality interaction in the lab

ns raise quality of care

ut the cost!

tors than any others in EU nations.

However, the country's medical lab system is highly structured and – due to low reimbursement rates – highly rationalised. In this ecosystem, the supraregional specialised lab as well as the onsite lab in in- and out-patient areas continue to fulfil important functions.

In Germany, lab physicians spearheaded digitisation by developing a comprehensive telematics infrastructure with electronic request and result transfer. The tightly knit network of transport services they organised ensures that, like urban patients, patients in remote rural areas share top diagnostic services – delivering the political promise of equal healthcare levels across the country.

Considering how this lab service infrastructure has evolved and is being further developed by lab physicians along with GPs and medical specialists, we can be confident that German quality of care is unmatched and prepared for future tasks.

Thus BDL clearly rejects any attempt to axe the requirement that lab physicians, rather than non-medical staff, should provide lab services. Even weakening the relationship of trust between lab physician and referring physician, BDL points out, puts quality of care at risk.

The constructive cooperation between physicians across disciplines will also be jeopardised when reforms in lab services are triggered merely for economic considerations – as was the case in the lab reform of 2018, which were driven not by the desire to improve patient care but to solve a reimbursement-related conflict between GPs and specialists when too many lab services are requested under budgetary constraints.

BDL thus demands a sustainable revision of this reform since necessary lab tests must not be discouraged by setting false economic incentives. It is not lab services that make healthcare expensive; it is therapies that are plain wrong, or therapies initiated too, that let costs spiral out of control. Despite the moaning about increasing lab costs, tests as well as reimbursement levels for lab physicians' services hover at the lower levels, compared to other European countries. Moreover, for many years lab costs reimbursed by the statutory health insurers have increased at a slower rate than healthcare costs in general.

* A laboratory physician has trained in scientific biomedical investigation and pathology and/or laboratory medicine, often with clinical subspecialty training.

allenges

context from real-world usage, and can provide unparalleled insights. For this, we have an arsenal of different methods that come into play, from user experience or fields like design thinking.'

So, how will this shape/change the lab environment?

Schuller believes that, with a better understanding of users, and improved interactions towards the systems, a lab environment can be created that provides a more positive user experience and, in the medical field, offers a better service to patients and hospital systems. It will also foster creativity and communication, strongly impact on the engagement and brand impression, and provide a positive interface towards a customer – or the patient.

There will also be an impact on personnel and workflow, such as improved flexibility and more tasks interacted remotely, particularly where there will be collaboration with robots.

'We must design the work of the future as attractive as possible,' he concluded. 'Human-technology interaction is an important enabler for this. To get this right, the workers, customers and users of our systems need to participate in the design process.' (mn)

Sharing four crucial perspectives

Pre-analytics and patient safety

BD, a global medical technology company, participated in the 5th European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) conference on pre-analytical phase in Zagreb, Croatia, 22-23 March 2019. At the conference, they met with Steve McManus, Professor Ana-Maria Simundic, EFLM conference chair, Professor Mario Plebani and Dr Alexander von Meyer, member of the EFLM conference scientific committee.

Mr Steve McManus, of the Royal Berkshire Hospitals National Health Service (NHS) Foundation Trust, Reading, United Kingdom

Professor Ana-Maria Simundic, from the Department of Medical Laboratory Diagnostics, University Hospital Sveti Duh, Zagreb, Croatia

Professor Mario Plebani is at the Department of Laboratory Medicine, University-Hospital of Padua, Italy

Dr Alexander von Meyer, from the Institute for Laboratory Medicine, Kliniken Nordoberpfalz AG, Weiden, and Klinikum St. Marien, Amberg, Germany

Professor Simundic and Dr von Meyer belong to the EFLM Working Group for Pre-analytical Phase (WG-PRE). They gave us their views on patient safety, the pre-analytical phase and its impact on the emergency department (ED).

Healthcare's purpose is to maintain or improve patients' health. With the introduction of new technologies, medicines and treatments, healthcare is becoming more complex. There is growing awareness that human and systemic factors can harm patients through preventable adverse events. Medical errors that lead to these adverse events are a major burden on healthcare systems across Europe. Up to 70% of all medical decisions are based on the results of laboratory tests and up to 66% of diagnostic errors occur during the pre-analytical phase. This is why these errors have the potential to cause great harm to patients according to Professor Plebani.

The challenge of haemolysis and other pre-analytical errors

For Simundic, there is a lot to be done to prevent pre-analytical errors in the ED. Haemolysis is by far the most frequent pre-analytical error and the main reason for rejected samples. It occurs when red blood cells rupture and release haemoglobin and other intra-cellular components into the plasma or serum.

Causes include drawing blood incorrectly, underfilling tubes, shaking of samples and using intravenous catheters to collect blood samples. Haemolysis may lead to unreliable results, delayed diagnosis and avoidable harm to patients. But, as Simundic pointed out during her presentation at the EFLM conference, not all clinical laboratories in Europe use the same haemolysis index cut-offs, or the same detection techniques. She pointed out that the visual detection of haemolysis has been found to be highly unreliable and extremely inconsistent.

According to Simundic and Plebani, the highest rates of haemolysis are in the emergency department (ED), with 65% of samples rejected for this reason. Simundic said the ED is the hospital department where most pre-analytical errors (e.g. patient misidentification) occur. Plebani found it is more difficult to identify haemolysis with point of care testing (POCT) than testing performed in central laboratories. With the rapid growth of POCT in clinical settings such as the ED, the role of the pre-analytical phase in POCT may therefore pose an increasing challenge. It is also common in the ED.

- Up to 70% of all medical decisions are based on the results of laboratory tests
- Up to 66% of laboratory errors occur during the pre-analytical phase
- Up to 65% of emergency department sample rejection is due to haemolysis

Measuring pre-analytical quality

Pre-analytical quality indicators are used to measure performance in the ED and other hospital wards. Dr von Meyer identified the most important quality indicator for healthcare systems as being turnaround time (TAT). Though definitions vary, we define it here as the time from test request to reporting of results.

von Meyer mentioned that we do not always know the exact sampling time, and this is important for calculating TAT. Some reference values are correlated to the time of day and sampling time is needed to calculate drug doses. However, clinical laboratories do not agree on a standardised way to use quality indicators to measure laboratory performance during the total testing process (TTP).

Preventing errors and improving pre-analytical quality

Solutions exist to reduce pre-analytical errors and positively impact on patient safety. Better haemolysis management requires using automatic detection systems instead of visual identification; defining haemolysis index cut-offs based on biologically variable data instead of using one cut-off for all tests and all patients, and informing clinicians when results are from haemolysed samples. If automatic detection systems are not available, the laboratory should use a colour chart for visual identification.

Von Meyer stressed the importance of knowing sampling time to improve TAT and to ensure sample stability. The exact sampling time should be documented and included with each sample. Faster TATs may lead to more timely treatment and improved clinical outcomes. Techniques used to reduce centrifugation time may also have an impact on TAT.

Since 2008, Plebani's team has been working on the harmonisation of quality indicator management. Over the past five years, laboratories have uploaded data on the model of quality indicators (MQI) website: http://217.148.121.44/ MqiWeb/Page_Presentation.jsf. This is a free service.

Plebani's team has collected and analysed this data, from which they have identified 26 quality indicators and 53 measurements, with defined benchmarks. Their final goal is to create an MQI that could be used by clinical laboratories all over the world to help increase sample quality while reducing laboratory errors.

Future perspectives: POCT testing and a culture of safety

For von Meyer and Simundic, the future of pre-analytics will be in POCT. POCT has been shown to reduce TAT, while providing rapid answers for decision-making in the intensive care unit (ICU). However, it presents specific challenges because POCT sample collection is usually performed by clinical staff who have varying levels of experience with sample analysers.

Care settings where POCT is used tend to have heavy workloads and the pre-analytical phase varies from patient to patient, based on level of urgency. This makes minimising human error an added challenge. Effectively training clinical staff in quality control and ensuring close collaboration with laboratory staff are important to maintain the reliability of results from POCT.

According to Mr McManus, learning is at the heart of a culture of safety. By learning from mistakes and applying that knowledge to workflows, we can improve patient safety. McManus and Simundic also said it is important to create the right conditions for this kind of organisational culture. Healthcare workers and laboratory staff should feel comfortable about reporting errors and suggesting ways to improve these workflows.

Another way to improve patient safety during the pre-analytical phase is through clinician-lab cooperation. A recent study by McKeeman et al showed that having a laboratory technician processing samples in the ED can reduce TAT and improve communication with the laboratory. Clinicians should feel free to come to the laboratory and lab workers to meet with their colleagues in care settings to improve communication between these important stakeholders along the care continuum and enhance patient safety.

Preventing haemolysis, keeping TAT as short as possible, reducing pre-analytical errors, harmonising quality indicators, maintaining the reliability of POCT results and building a culture of safety are all ways to ensure patient safety throughout the pre-analytical phase in the ED and beyond.

*References may be requested from the author

Discover BD Patient Safety: eu.bd.com/patient-safety

Switching off chronic inflammat

The transcription factor GATA-3

Source: Shutterstock/VectorMine

Chronic inflammatory diseases, such as allergies and asthma, are not only an acute problem but also a major research and prevention challenge. When our EH correspondent spoke with Professor Harald Renz, Director of the Institute for Laboratory Medicine at the University Hospital Gießen/Marburg, Germany, they discussed the major reason for increases in the number of these widespread diseases.

Interview: Walter Depner

'Allergies such as asthma, neurodermatitis and hay fever,' observed Professor Harald Renz, 'are so-called non-communicable diseases – NCDs. All NCDs, including auto-immune, cardio-vascular and neuropsychiatric diseases, are rising worldwide. This group of diseases is associated with a genetic disposition. Genes, however, do not lead to the outbreak of NCDs, including allergies. Outbreak is triggered by certain environmental and lifestyle factors.

'Most experts seem to agree that NCDs, and thus allergies, are increasing because the lifestyles in the Western industrialised world poses a major challenge for the immune system: it produces an abnormally vigorous response to rather benign environmental substances, the allergens. Why this excessive reaction? Due to the Western lifestyles the immune system lacks sufficient training, particularly during childhood. This training is necessary to induce immunological and clinical tolerance. Microbes, harmless bacteria from the environment, trigger tolerance induction.'

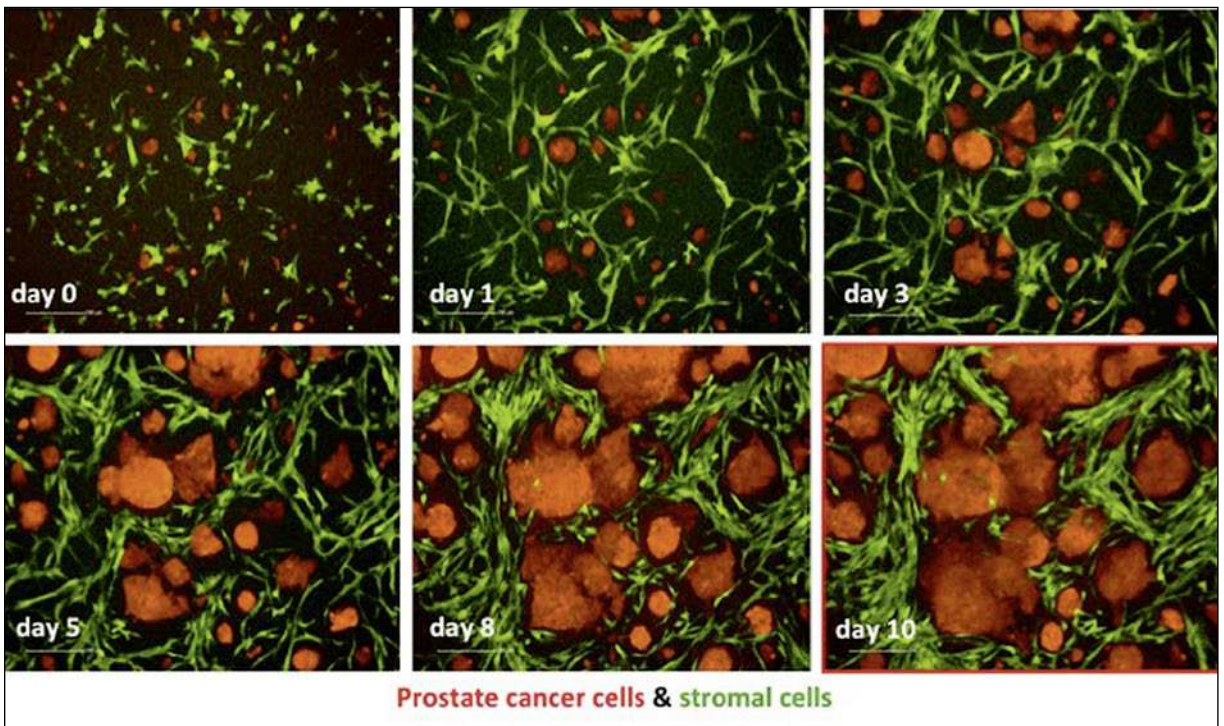
Figures and stats?

'Since World War II, the prevalence of allergies has been escalating significantly – in the Western industrialised world. We estimate that each third child is born with an allergy risk. Recent studies at the Robert Koch Institute show this increase to continue unabatedly. Approximately 10 percent of the population suffer

Quantitatively assessing tumour cell differentiation

The potential of high-content screening

The key challenges faced by High-Content Screening (HCS) and its potential for personalised medicine were outlined at the recent SLASEurope 2019 event, in Barcelona, by Professor Matthias Nees from Finland's Institute of Biomedicine, in the University of Turku.



Spontaneous formation of tissue-like structures from stromal cells (green) and tumour cells (red), when embedded between two layers of extracellular matrix in 3-D culture. Single tumour cells generate multicellular tumour organoids, which are surrounded by stromal cells in a fashion typical for solid cancers, such as prostate cancers.

Report: Mark Nicholls

HCS is used in biological research and drug discovery to identify active pharmaceutical ingredients (API) such as small molecules or peptides that alter the proliferation (growth), survival or the phenotype of cells. Increasingly, HCS is performed not just with isolated cells but with living multicellular structures (organoids) or tissues.

'The basic message of my talk related to the necessity to provide tumour cells with context, namely extracellular matrix and the tumour microenvironment,' Nees explained. 'This is necessary because solid cancers, particularly the most common ones (epithelial cancers or carcinomas), always contain these components as part of their tissue architecture.'

Isolated tumour cells growing on plastic surfaces, he explained, strongly tend to hyperproliferation and acquire properties that have little in common with the behaviour of tumour cells in a patients' tissues, whereas if extracellular matrix (ECM) is added, tumour cells can partially differentiate and form polarised tissue-like structures.

Revolution of cell biology

'These are the equivalent of "organoids", now widely used in research and personalised medicine,' Neels explained. 'Organoids and related 3-D culture methods that also contain other cellular components of tissues – such as the stromal fibroblasts, or immune cells –- may revolutionise cell biology.'

However, he acknowledges they are still currently short of being utilised in HCS as the complexity of such 3-D cultures is considered too high for the generation of robust reproducible assays and there is a lack of appropriate automated image analysis tools to make sense of the complexity observed in such 3-D tissue cultures.

He stressed that the right choice of ECM is critical to trigger a degree of differentiation or maturation in vitro that corresponds to genuine tissue structures observed in cancer biopsies.

Use of liquid handling robotics

However, even with these more complex tissue-models, there are only very few tools that allow quantitative evaluation of phenotypic drug effects on both tumour and stromal cells in such 3-D microtissues.

During his talk, Nees demonstrated how to mimic the generation of miniaturised, tissue-like structures in vitro. These microtissues can be generated in 96- and even 384-well plates; liquid handling robotics can be used, and they can be scaled for higher throughput. 'Simultaneously, we demonstrated that high content imaging and automated image analysis software can extract the most important information from both tumour and stromal cells, about their chemosensitivity towards therapeutics for example. In fact, it can extract so much information, that it is required to focus on the most relevant morphologies and living versus dead cells.'

His team has quantitatively measured drug effects on growth and proliferation of tumour cells (organoids) and surrounding stromal structures, but also cell death and their invasive properties. 'This,' he pointed out, 'can be used in drug screening, such as with cancer cell lines, but also in personalised medicine, in which primary tumour cells are used instead - in the same 3-D systems.'

Main benefit: Exclusion of the risk factor

'There is a suggestion that about 20-30% of patients respond to chemotherapeutic drugs that they are given and 70-80% do not respond, or poorly respond, so there is a risk that you are treating patients with a drug that does not work, or miss a patient who would have responded to a particular drug. The main benefit is to exclude this risk factor.'

Potential: Chemosensitivity assays with patient cells

This research has occupied Nees Finland team for the last decade. While chemosensitivity assays with patient cells or tissues are not widely established in clinics due to a lack of validated assays, the field does have potential.

Ideally, Nees added, this could be combined with genetic tests for cancer mutations, which is increasingly accepted as a predictive tool for informed clinical decision-making. A combination of both approaches would be ideal.

In generating complex 3-D cultures, his team discovered that different tumour types form very different multi-cellular tissue-like structures in vitro, leading to the research focus on invasion.

The stroma component, he explained, is critical for how aggressive a tumour cell becomes and also influences how a tumour cell responds to drugs. In terms of whether HCS can advance diagnosis and therapies associated with cancers, Nees believes it can 'broaden the scope of biology' that is examined.

'There are a number of other things that are normally difficult to look at,' he added. 'Differentiation of tumour cells is rarely looked at in other assays but, in HCS, you can assess that even quantitatively and see if they form round structures or a particular texture, which tells you immediately that tumour cells are differentiating – not invading.'

Tumour differentiation is a key issue

Tumour differentiation, he explained, is a key issue that typically opposes aggressive features like invasion which. in turn, is strongly connected to metastasis and recurrent disease.

Cells often show an amazing degree of 'plasticity' and can readily shift between differentiation and invasion.

Professor Matthias Nees is Adjunct Professor in the Department of Biology at University of Turku in Finland, with a research interest in High Content-Screening (HCS). He aims for the development of complex, three-dimensional cell and tissue culture techniques that recapitulate the architecture of solid cancers. The focus is on tumour-host interactions, such as communication between cancer and stromal cells (tumour micro-environment TME), and the extracellular matrix (ECM). From 2005-2014 he was Group Leader and Principal Investigator at VTT Technical Research Centre of Finland OY, Turku (Teams: Systems Biology and Cell Culture Model Systems).

ions

from asthma, the most severe manifestation of the respiratory tract. Moreover, food allergies are rising.'

What about new strategies, pharmaceuticals, therapies, prevention, and so on?

Prevention is in the early stages and still largely neglected, on the clinical and political level. For the general practitioner (GP) prevention doesn't pay because it's poorly or not reimbursed at all. However, the pharmaceutical industry is developing new medications, based on improved knowledge about inflammatory response at the root of the diseases. These pharmaceuticals are very effective in containing the inflammatory response, but they are also very expensive.'

You have spoken about new pathophysiological concepts for asthma and allergies; do these include new diagnostics and medication?

'We've been working on the development of an active substance to control the main switch of allergic inflammatory reaction – the transcription factor GATA-3. Our approach from day 1 was to neutralise this intercellular messenger via an intracellular attack on the level of the so-called messenger-RNA, which is a stage leading to the synthesis of the GATA-3 protein. Our clinical data on asthma, as well as on a special form of COPD and, most recently, ulcerative colitis, show unambiguously the effectiveness and safety of this approach. Nevertheless, larger studies are required to document the broader efficiency in more detail.

'Currently, this molecule is being further developed by the start-up sterna biologicals. It is very impressive to see that today a molecule is available that's based on an idea that's been maturing for 20 years – a molecule which can be used in human patients and which has positive effects.'

In 2017 you and Professor Holger Garn jointly received the Paul Martini Award for your work on new allergic asthma medication. The substance you developed prevents certain immune cells from using a specific gene involved in the disease. How is this progressing?

'It was an honour to receive the award for our group's work in pharmaceutical development. More than 20 years ago – still at Charité in Berlin – my group looked into possibilities to use a then newly discovered main switch for allergic inflammatory reactions in new medication. Since this switch is within cells, we needed a substance that is effective on the cell level. We opted for a then innovative way: to address the messenger RNA – the mRNA.

'It took over a decade to launch the first clinical study, initially with healthy subjects, to test the therapy's safety. Later we included subjects suffering allergic asthma. Today we are about to test this therapy approach in larger studies and for other pathologies largely regulated by this main switch, the transcription factor GATA-3.'

What can you forsee in this field in the future?

'I can imagine that, in ten years, we will have something like an allergy vaccine, very much like our vaccines against infectious diseases today. But that's still a long way to go.'

Professor Harald Renz trained at the National Jewish Medical and Research Centre in Denver, Colorado (1989-93) and Charité in Berlin (1993-99). He now directs the Institute for Laboratory Medicine at the University Hospital's locations Giessen and Marburg, where he researches chronic inflammatory diseases. He he is a representative and is a representative of the German Centre for Lung Research. Renz was also a Fulbright scholar and visiting Professor at Harvard Medical School and at Hadassah University Jerusalem.

Robotic surgery: good for some, not all

Myths and misconceptions

Report: Sascha Keutel

The first use of a robot-supported surgical intervention was reported in 1985, when the robot arm PUMA 560 placed a needle for a cerebral biopsy using CT guidance. Since then, strong growth in the market for robotic surgery has occurred, due to an increasing automation demand in the healthcare as a whole and greater concentration on minimally invasive surgery (MIS) for faster recovery.

Robot-supported surgery is now applied in many disciplines. In neurosurgery, for example, image-controlled robots aid in the examination of brain lesions without serious damage to adjacent tissue. General surgeons can perform gall bladder, hernia, cancer and colon operations with a robot. Robots are used in orthopaedic surgery to form the femur bone so that a prosthetic hip joint replacement fits exactly.

However, some patients still find the concept of robot operations unsettling or intimidating, not least because of a few widespread myths.

One such myth is that the procedure is programmed and the robot performs the operation on its own, automatically, without any human involvement. In reality, robot surgery is an operation that the surgeon performs aided by a robot system through which he controls 100 percent of what happens.


Source: Shutterstock/Master Video

Surgical robotic systems are composed of miniaturised surgical instruments mounted on robot arms. The surgeon controls every movement of the robot arm and instrument directly in real-time. Every movement the surgeon performs with hands on the console is performed simultaneously by the robot control. In other words, the robot acts as the extended arm of the surgeon. Another frequently propagated myth is that the surgeon performs the operation in another room. The surgeon is always present in the room and the console used to control the robot is only a few meters away from the patient. Moreover, the patient is constantly monitored by an assistant next to the bed, along with members of the anaesthesia team and a nurse.

The advantages

Robot systems permit outstanding visualisation and very precise movements. These properties enable the surgeon to perform minimally invasive interventions with high precision, control and flexibility. All this leads to a generally shorter hospitalisation, less post-operative pain and a faster return to active life compared to laparoscopy or open operations.

However, robot-supported surgical systems are expensive and, as a rule, require longer operating times as well as intensive training and frequent practice.

Often, the evidence for the advantages of such surgical techniques is unconvincing. The risks of robot-supported operations are comparable with those of common surgery. In fact, clinical studies of robot-supported surgery for indications in the chest and abdomen as yet have only exhibited a few advantages for this cost-intensive surgical method, according to a current analysis by the Ludwig-Boltzmann-Institute for Health Technology Assessment (LBI-HTA), in which the relevant international clinical studies have been assessed. 'Altogether, it can be said that, in the case of the indications analysed, there are few signs of clear advantages for the effectiveness and safety of this new surgical technique,' said PD Dr Claudia Wild, director of the LBI-HTA.

One example is a study by researchers for UNSW Medicine, at the Ingham Institute and the South Western Sydney Local Health District. These show that prostate cancer patients believed erroneously that the robot operation constituted a more definitive cure for prostate cancer than other treatments, such as radiation therapy. 'The robot-supported radical prostatectomy is becoming the treatment of choice more frequently by many men, despite the potentially higher cost and limited evidence of its superiority over other treatments,' Dr Ben Smith of the Ingham Institute pointed out.

The study also found that patients often disregard the various side effects of their treatment options but, above all, follow only their physicians' recommendations. However, robot technology might not be the right option for every patient. Therefore, patients ought to gather information about all treatment options before they make a decision that has a substantial impact on their quality of life.

Surgical breakthrough in France

Robot enables lumbar spine repair

Is it possible to repair the rachis without having to open the abdomen or the back? A team of French surgeons has done just that. Thanks to minimally invasive robotic surgery, exposing the patient to risky spine interventions may soon be avoidable, a leading surgeon explained.

Report: Mélisande Rouger

Neurosurgeons and vascular surgeons in France have, for the first time, successfully repaired the lumbar spine with the help of a da Vinci robot. This pioneering intervention results from a cooperation between Nancy University Hospital and Timone University Hospital in Marseille. The patient, a 36-year-old man with a complex vertebrae fracture caused by lumbar trauma, received an iliac bone fragment implant and prosthesis and is recovering quickly.

This minimally invasive robotic technique is a game changer in spine trauma surgery, which traditionally requires opening the patient quite extensively either in the abdomen or the back, to access the lesion and secure the surrounding vertebrae, aorta and blood vessels.

With this new type of surgery, surgeons can now repair the fractured or damaged vertebrae by doing an incision of just a few millimetres, Serguei Malikov, professor of vascular surgery at Nancy University Hospital, explained.

'We did the same radical and final gesture as in classical surgery, only with a simple puncture of the abdominal wall. We did not have to open the wall to repair the rachis,' he said. 'We just placed the robot's arms inside the cavity, without damaging the abdominal wall or moving the organs.'


From left, the robotic spinal surgery team. Neurosurgery - Professor S Fuentes, Doctor N Mansouri. Vascular Surgery - Professor S Malikov, Doctor N Settembre, Doctor C Saba

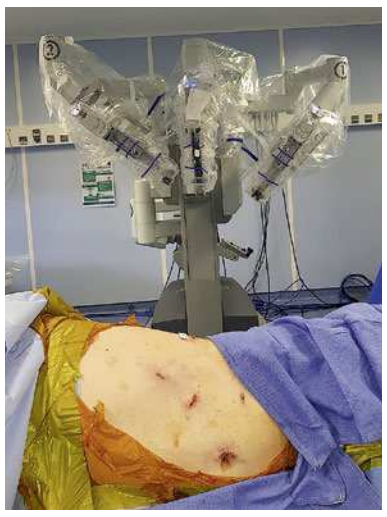

A surgeon controls the robot via a control console

Like seeing spine and nerves under a microscope

Working with the robot tremendously improves surgical vision during the intervention, thanks to a powerful camera, excellent resolution and the possibility to zoom in. 'It's like seeing the spine and the nerves, the part that wraps up the bone marrow, through a microscope,' he said, adding, 'with much more detail than traditional surgery,'

Robotic surgery is fast and expands the surgeon's field of action without touching surrounding tissues. 'The robot improves our precision and movement amplitude, allowing us to repair areas that used to be complicated to access,' he said.

With the robot, the minimally invasive approach is as radical as surgery, but without any risks. The intervention time is shorter and the patient does not need to be opened and closed, prompting better surgical outcome and earlier recovery.


The da Vinci assisted in an anterior lumbar repair

Cooperation is key

Experts foresee a wide variety of applications for repair of rachis lesions caused by trauma, infection, degeneration or cancer. Robotic surgery of the spine is bubbling. Other patients have been treated with the technique in Nancy and Marseille. Their evaluation will help determine how much the technique can be expanded to wider surgical practice.

As for the lumbar spine in particular, Malikov said he found only two publications – in the USA but none in Europe – on similar interventions, but at other rachis levels.

Serguei Malikov studied medicine at the University of St Petersburg, Russia. He carried out his research in experimental surgery in Marseille and currently heads the Vascular Surgery Department in Nancy University Hospital, France

In France, vascular surgery has been a well-established subspecialty (founded 1984) much earlier than in other European countries. This seniority, combined with the possibilities offered by technology, is promising, and boosts collaboration with other subspecialties, especially neurosurgery, Malikov believes.

'We are very proud of our breakthrough. We've been working on the topic for the past five years, first in animals, then cadavers.

'It's the result of a close cooperation between two hospitals, and two subspecialties: neurosurgery and vascular surgery. The key in rachis reconstruction is vessels and aorta control. It's the access, not the disease, that demands vascular surgeons to step in.'

Experimental works have been carried out at Nancy Surgery School, within the Lorraine Virtual Hospital, a reference centre in Europe for training and research in medico-surgical innovation (notably telesurgery, robotic, coelioscopic, endoscopic and endoluminal surgery) and evaluation of therapeutic processes validation based on surgical expertise.

New robots promise to improve spinal straightening

A precision greater than humanly possible

Report: Mark Nicholls

ScoliBot, a new robotic system, could perform spinal surgery to a higher degree of accuracy than human counterparts. Devised by a team from Nottingham Trent University (NTU), the system has two robotic arms that semi-autonomously drill holes in individual vertebrae in procedures to straighten the spines of patients with conditions such as scoliosis or kyphosis.

Leading the project, Professor Philip Breedon, head of NTU's Medical Engineering Design Research Group, says the technology could deliver higher levels of accuracy than achieved previously as a result of the robotic arms being able to move in unison and naturally with the patient's spine during the operation while drilling.

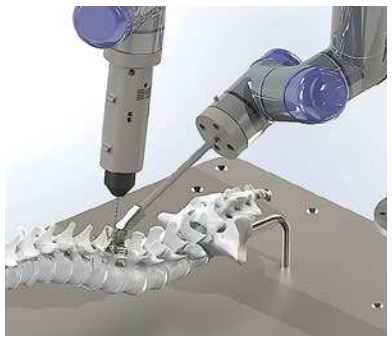
'Surgeons performing life-changing operations to correct spinal conditions have to ensure pinpoint levels of accuracy to avoid causing unnecessary and potentially serious injuries,' he stressed.

Robotic teamwork

'This technology promises to deliver greater levels of accuracy than ever previously achieved – or even humanly possible – to improve the safety and efficiency of such procedures that are needed by people with serious spinal conditions.'

The holes drilled in the vertebrae are used to insert pedicle screws, which are attached to deformity rod reducers that allow surgeons to lever individual vertebrae and realign the spine. Known as the datum and tooling robots, the two robotic arms work in collaboration during the procedure. The datum robot is secured to vertebrae and moves with them to follow the natural movements of the patient, instantly relaying data on this movement to a computer. The tooling robot then adjusts automatically so that it remains on its pre-defined path and continues to drill accurately.

Philip Breedon demonstrating the two robotic arms for spinal surgery



Closeup of the robotic arms

Reduction of surgery time

The patient could benefit because the robot's reliability and precision will enable specific surgical steps to be performed more precisely,' Breedon observed. 'Ultimately, the aim is also to reduce surgery time.'

The research also explores the use of augmented reality (AR) to provide surgeons with live visual feedback to illustrate the depth of each hole as it is drilled in real-time. Accuracy of drilling has been recorded at 0.1 of a millimetre.

'The control system will engage with the patient's body by providing a superimposed image on the surface of a patient, or in the visual field of the surgeon utilising wearable technology,' Breedon added. He is working closely on the project with Professor Bronek Boszczyk, Head of the Spine and Scoliosis Centre, Schoen Clinic, Vogtareuth, Germany, and Nottingham University Hospitals Trust UK, who explained that the system also offers potential advantages for the surgeon. 'Certain surgical steps can be quite physical for the surgeon and fatiguing,' he said. 'The introduction of the robotic system means that surgery could be performed without any muscle tremor, very precisely and without fatigue often associated with repetitive tasks.

Total accuracy required

'The robot, or robots, could also be useful as a "surgical assistant". This is another area of research and development we are currently exploring. It's paramount that spinal procedures are carried out with total accuracy in order to minimise what can be substantial risks to a patient. This technology has the potential to minimise those risks by performing a key part of the operation with accuracy that cannot be achieved by a human hand.'

Describing it as 'a brilliant example of how robotics can enhance and improve the way in which intrusive operations are carried out', he said the system can improve patient safety and whilst ensuring efficiency of process.

While the development team sees the current system best linked to surgical interventions on bones, because they provide a hard interface for the robot to engage with, they also envisage that the collaborative robotic system in the future could be used in endoscopy and keyhole procedures.

Philip Breedon is Professor of Smart Technologies at Nottingham Trent University and leads the Medical Engineering Design Research Group. His research interests centre on new and emerging technologies and materials, including wearables, 3-D printing of pathological models, the surgical pathway additive and subtractive manufacturing for medical applications, biomimetics, surgical robotics, and extended reality systems.

Professor Bronek Boszczyk is Head of the Spine & Scoliosis Centre, Schoen Clinic, Vogtareuth, Germany and Honorary Clinical Associate Professor at the Division of Orthopaedic and Accident Surgery and a Visiting Professor to Nottingham Trent University. His research focuses on spinal disorders.

Aiding well-being and future surgical training

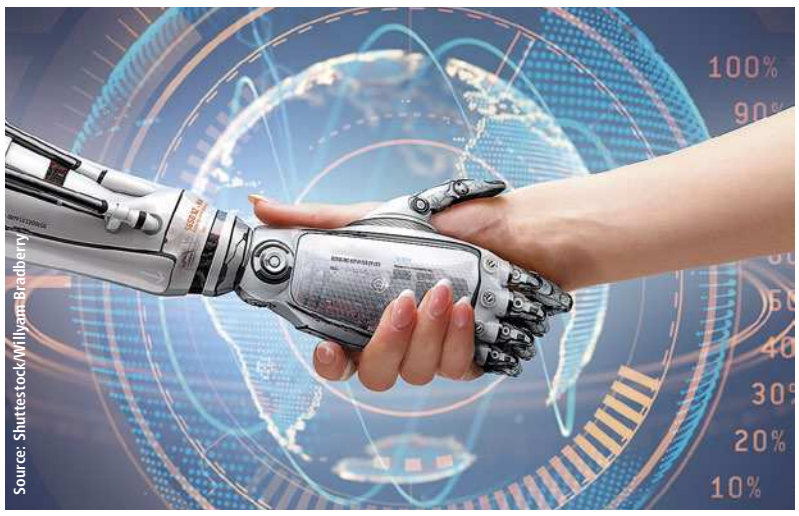
Robotic surgery is expanding

Report: Mark Nicholls

Standardisation of robotic surgery procedures is seeing increased usage and improved outcomes for patients and could also play a role in helping with the overall well-being of surgeons in terms of, for example, ergonomic benefits that could reduce repetitive strain injury (RSI) and back conditions.

Change of surgical care

Richard Kerr from the Royal College of Surgeons (England) recently chaired the RCS Commission on Future Surgery, which focused on advances in medicine and technology, plus robotics, that are likely to change surgical care in the next 20 years. Areas considered included innovations in data analytics, artificial intelligence, genomics, regenerative medicine, virtual and augmented reality, 3-D printing and planning.



Source: Shutterstock/Wilyam Bradberry

'Perhaps the most important thing to say is that the use of a robot effectively adds to the surgical armamentarium," Kerr explained. "It's about adding to the instruments that we have available to help patients, not about robots doing operations in isolation from surgeons. This is a very sophisticated tool, where the surgeon is in an ergonomically-comfortable position. It's a very precise instrument and therefore eliminates any sort of human frailty like tremor or fatigue.'

Lengthy surgical procedures can be physically tiring; surgeons move into awkward positions to gain a line of sight into a patient, or they use microscopes or manipulate instruments during laparoscopic procedures. Using a robot, the surgeon is seated in front of a screen and can manipulate the robotic arm with his hands from a console.

'You have a very precise instrument that you can navigate to difficult spaces and places within the human body, which gives us improved access, visualisation and illumination,' Kerr pointed out. 'Because you are using minimally invasive techniques, it's also a huge benefit to the patient, hopefully with improved recovery times and less pain. What's also important is that there is the potential to use robots to begin to standardise what we surgeons do.

"Naturally, there's a variation in outcomes. I think use of the robot potentially allows us to reduce the variation and hopefully improve the level of care that we give patients."

Training platform

'The training issue is very important. We need to ensure there is a defined training platform that makes sure that we can reap all the benefit and hopefully eliminate any of the risks that come with bringing new technology into our ways of working.' And, Kerr emphasised, 'I think the take-up of robotics needs to be conducted in a structured way, with a structured training programme.' RCS England is keen to work with NHS England to achieve this.

In conclusion, the neurosurgeon sees the use of robotic surgery expanding from the more commonplace use in urology to colorectal surgery, gynaecology, cardiothoracic surgery, ophthalmology, and potentially into his own field: neurosurgery.

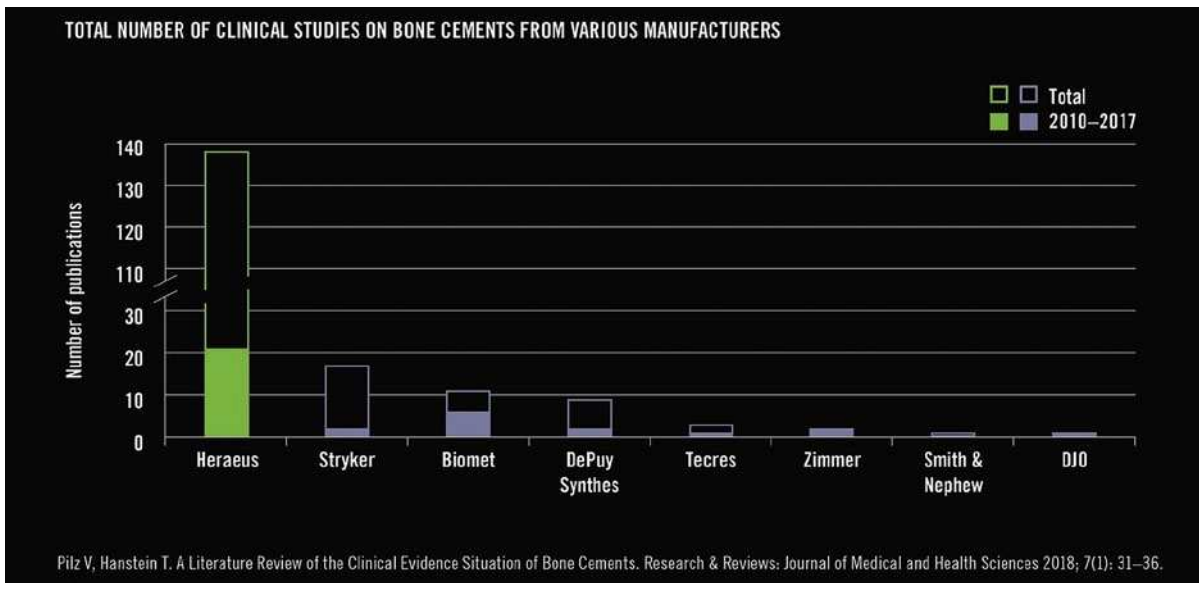
Neurosurgeon **Richard Kerr**, at the John Radcliffe Hospital, Oxford, has been a consultant for 30 years. He devised and ran the Oxford Skull Base Practice and his subspecialty interests lie in skull base tumours, oncology and vascular disease. A former president of the Society of British Neurological Surgeons (SBNS), he sits on the council of The Royal College of Surgeons of England and chaired the independent Commission on the Future of Surgery.

The vital element in successful joint replacement

Bone cement: a key factor

Bone cements made of polymethyl methacrylate (PMMA) are well established in joint arthroplasty, particularly for hip and knee joint implantations. PALACOS was introduced in 1959 as one of the first bone cements and has proven very successful to this day.

The history goes way back. The first patent based on cold-curing plastics was issued in 1943. No one had any idea that this would lay the foundation for the unique success story of bone cements in orthopaedics.



Pilz V, Hanstein T. A Literature Review of the Clinical Evidence Situation of Bone Cements. Research & Reviews: Journal of Medical and Health Sciences 2018; 7(1): 31–36.

The bone cement breakthrough in orthopaedic surgery happened in the 1950s to anchor acrylic glass caps to the femoral head after removal of the joint cartilage.

After further product development, the first bone cement for orthopaedic surgery was launched in Germany in 1959 under the name Palacos. The brand has since become the gold standard among bone cements.

Following an idea from the Hamburg surgeon Professor Hans Wilhelm Buchholz, antibiotics were added to this bone cement for the first time in 1969. Palacos R with gentamicin has been available since 1972, as the first antibiotic-loaded cement produced commercially with added gentamicin.

Evidence as the basis for quality

The development of Palacos bone cement is founded upon numerous clinical studies and investigations to achieve the desired medical and mechanical properties of the cement. Factors such as strength, creep resistance and longevity are relevant to ensure optimal load transfer of the endoprosthesis to the bone. Decisive factors for the highly reproducible and reliable quality of the cement are the special polymer structure and the manufacturing and sterilisation process used and validated by Heraeus Medical, which has remained unchanged since its introduction in 1959.

The most studied bone cement worldwide

Numerous registers, meta- and long-term studies from the past decades document that cemented knee and hip joint prostheses, especially for an older population, have considerably longer survival rates and reduce the risk of revision. In particular, Palacos products with antibiotic additive are superior to other bone cement manufacturers thanks to their longer and higher antibiotic release, the manufacturer adds.

'Over the past 60 years, Palacos has been used with and without antibiotic additives in more than 30 million joint replacement procedures worldwide. Palacos cements are therefore the most frequently used bone cements to date – in more than 90 countries,' Hereaus confirms.

The reproducible quality of this cement is documented by evidence from more than 130 clinical studies published since the 1950s in renowned international scientific publications and involving over 9,000 patients, the firm adds. 'The first long-term studies on the use of Palacos were already available in the 1980s, and no fewer than 20 studies have been added since 2010. A literature analysis from 2018 shows that Palacos is not only the most often used bone cement in the world, but also the best investigated.'

Committed to the gold standard

'Cements with different properties are needed depending on the field of application in joint arthroplasty. Users can now turn to Palacos cements in various viscosities (flow properties). The high- and medium-viscosity variants, for example, are fast-curing and can be inserted easily into the bone or applied to the implant,' Heraeus reports.

Additionally, the company confirms, handling and mixing of Palacos has been further simplified and the portfolio also supplemented by the modern ready-to-mix Palacos pro system.

* Source: Heraeus Medical

Assisting middle and inner ear microsurgeries

Cochlear implant procedure progresses

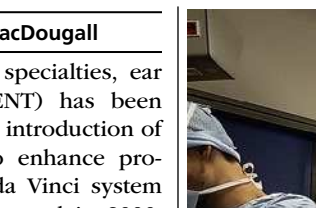
Report: Jane MacDougall

Unlike other surgical specialties, ear nose and throat (ENT) has been poorly served by the introduction of robotic platforms to enhance procedures. Since the da Vinci system first gained FDA approval in 2000, robot-assisted surgery has become commonplace in many specialties, including neurology, urology, etc. with numerous other general surgical applications. However, existing systems including the da Vinci are not easily exploitable for the microsurgical techniques used in inner and middle ear procedures.

Realising this unmet surgical need has driven Professor Yann Nguyen to pioneer the development of a robotic system, designed to meet his specific needs. In collaboration with engineers from the Sorbonne University, Inserm, and Collin SAS, a French company specialising in devices and instruments for use in ENT, with additional funding from a private foundation for hearing (Fondation Pour l'Audition), RobOtol, was created.

First developed in 2009, this robot is suitable for use in otolaryngology surgical procedures such as stapedectomy, ossicular chain reconstruction, tympanoplasty, myringotomy and mastoidectomy.

The system gained CE approval in 2016 and, since February 2018, Nguyen's surgical team has used one of these robots on an almost continual daily basis.



Nguyen performing robot-assisted middle ear surgery

Ossicular chain reparation

Reducing collateral damage

This July, for the first time globally, Nguyen used the RobOtol to insert the electrodes for a cochlear implant. Cochlear implantation itself is not new. First attempted more than four decades ago, it has been widely practiced for the past 25 years. The process involves replacing the role of the cochlea in hearing with an electrode array inserted into its immediate vicinity, which picks up electric currents from the conversion of sound waves directed by an externally placed microphone and processor. The auditory nerve is stimulated by these electric currents and transmits nerve impulses to the brain, where they are interpreted as acoustic sensations.

This microsurgery is normally carried out within a few hours as an out-patient procedure, under general anaesthetic. During the operation an electronic receiver (processor and antenna) is placed five mm under the skin and attached to the skull just behind the ear. An opening is created from the implant to the cochlea by drilling a three cm channel through the temporal bone to enable the passage of the device's electrodes to the cochlea.

Ten patients from Berne in Switzerland have been operated on using a robot for this initial drilling phase, achieving accuracy that was unthinkable until now. However, for Nguyen this is not where a robot offers any advantage over a human in terms of outcome. For him, the part of the operation where the development of the RobOtol is so essential is so pass electrodes through the cochlea, which resembles a snail's shell in structure, without causing unnecessary damage to the integrity and functions of this, even in profoundly deaf subjects, still vital organ.

Robot-assisted ENT surgery using the specialised system

No visual guidance

Additionally, the surgeon has no visual guidance at this stage because visibility is lost once the entrance of the cochlea has been passed and the trajectory of the electrodes is aided only by the surgeon's touch. Nguyen stresses that this insertion of electrodes needs to be performed as slowly as possible to preserve the organ, and reduce inflammation, fibrosis and scarring to speed recovery and obtain the best possible outcomes.

His reasons for requiring this improvement are compelling. First, because the implant life is approximately 20 years, some patients, especially children, will need multiple procedures during their lifetime. Therefore, his aim is to inflict the minimal mechanical trauma possible with the first implantation, so as not to jeopardise the outcome of any second or even third future procedure. He also hopes that, in the longer term, solutions such as gene therapy and stem cell transplants will become a reality for restoring hearing among these patients, which is why he wants to retain the maximal integrity of the inner ear so that those he operates on today will not be excluded from future developments because of damage caused when they were younger.

Worldwide, two other RobOtols are in current use, one at the University Hospital of Liège in Belgium; the other in Shanghai, China. The fourth and most sophisticated machine is in the laboratory where it serves as a prototype to develop new procedures, such as this latest cochlear implant. The implants available today are all for manual use, but Nguyen is confident that, once more surgeons use the robot for this procedure, implant manufacturers will be keen to adapt their devices for robotic use.

Slow and steady

Using robot-assistance for a cochlear implant means that the electrodes can be placed at speeds as low as 0.1 sec/min with no tremor – something a surgeon would be unable to do. While adding a few seconds to the operating time, this slow advance of the electrodes is paramount to minimising trauma. Additionally, the robot can use more senses than a human in this environment. With no visual control, the surgeon is dependent on touch alone and, however good they are, their reactions to any impediment are slower by several milliseconds than a robot's. With future improvements, the latter will be able to use heat sensitivity, measure hearing in real time and react instantly to any problem, thereby increasing the accuracy of procedures in a way no human can achieve.

According to Nguyen the RobOtol represents one of the first breakthroughs in cochlear implant surgery for 20 years. He considers that, until now, the technique had plateaued and was relying purely on the surgeon's experience but now, thanks to these developments in robotic-assistance, the procedure has been forced into the 21st century and will remain state-of-the-art until an as yet un-invented technology supersedes it.

Yann Nguyen MD PhD is Assistant Professor in the ENT Department, Otology Unit, Auditory Implants and Skull Base Surgery, at Pitié Salpêtrière Hospital, Paris. Prior to this, he was resident otorhinolaryngologist in the greater Paris public hospitals (AP-HP). In addition to his doctorate, he is a a specialist post-graduate in ENT, Head and Neck Imaging, Surgical Robotics and ENT, Head and Neck Cancerology. He has authored more than 50 papers, plus three patents and has won awards for pioneering work in robotics for ENT. Since September this year he has been promoting the use of robot-assisted surgery in inner and middle ear surgery via a club for current users and potential customers of the RobOtol system.

Light and magnets to control and reconfigure soft robots

Creating a true transformer

The movement of soft robots can be remotely controlled to lock them into position for as long as needed and later reconfigure them into new shapes. Developed by researchers at North Carolina State University and Elon University, the technique relies on light and magnetic fields. 'We're particularly excited about the reconfigurability,' says Joe Tracy, a professor of materials science and engineering at NC State and corresponding author of a paper on this work.

'By engineering the properties of the material, we can control the soft robot's movement remotely; we can get it to hold a given shape; we can then return the robot to its original shape, or further modify its movement and, we can do this repeatedly,' he explained, adding: 'All of those things are valuable, in terms of this technology's utility in biomedical or, for example, in aerospace applications." For this work, the researchers used soft robots which were made of a polymer embedded with magnetic iron microparticles.

Under normal conditions, the material is relatively stiff and holds its shape. However, researchers can heat up the material using light from a light-emitting diode (LED), which makes the polymer pliable. Once pliable, researchers demonstrated that they could control the shape of the robot remotely by applying a magnetic field. After forming the desired shape, researchers could remove the LED light, allowing the robot to resume its original stiffness – effectively locking the shape in place.

By applying the light a second time and removing the magnetic field, the researchers could get the soft robots to return to their original shapes. Or they could apply the light again and manipulate the magnetic field to move the robots or get them to assume new shapes.

In experimental testing, the researchers demonstrated that the soft robots could be used to form 'grabbers' for lifting and transporting objects. Soft robots could also be used as cantilevers, or folded into 'flowers' with petals that bend in different directions.

'We are not limited to binary configurations, such as a grabber being either open or closed,' says Jessica Liu, first author of the paper and a PhD student at NC State. 'We can control the light to ensure that a robot will hold its shape at any point.'

Additionally, the researchers developed a computational model that can be used to streamline the soft robot design process. The model allows them to fine-tune a robot's shape, polymer thickness, the abundance of iron microparticles in the polymer, and the size and direction of the required magnetic field before constructing a prototype to accomplish a specific task.

Rotation of a "flower" with six petals.

'The next steps include optimising the polymer for different applications,' Tracy says. 'For example, engineering polymers that respond at different temperatures in order to meet the needs of specific applications.'

Multidisciplinary care is key to cardiac disease management

Research with 7-Tesla MRI

New 7-T MR methods could potentially shed light on cardiomyopathies' principles, according to a leading French radiologist who also stresses the importance of teamwork between radiologists, cardiologists, surgeons and anaesthesiologists.

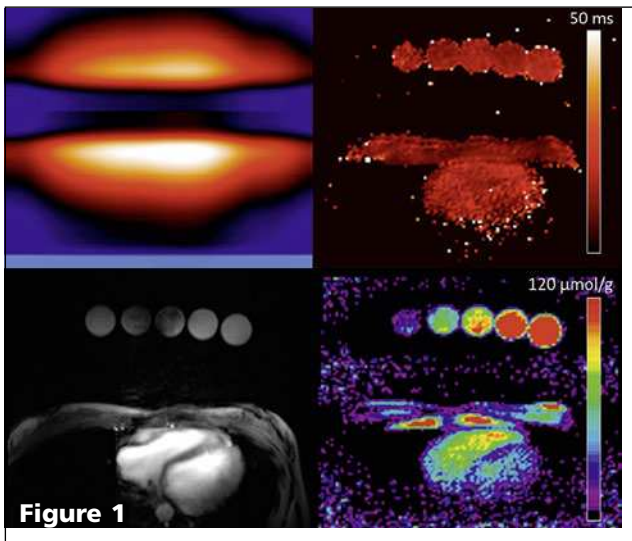


Figure 1

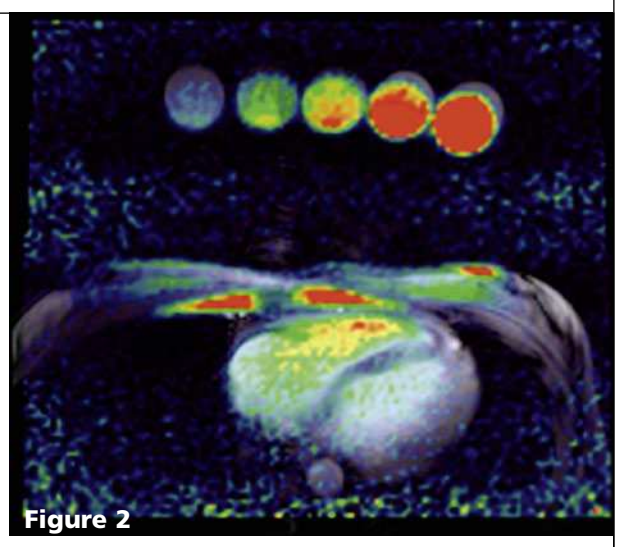


Figure 2

Sodium mapping of the heart using 7-Tesla MRI

Higher signal-to-noise ratio (SNR) using 7-Tesla MRI allows to map sodium in the human heart. The isolation of the long relaxation sodium component (using a long echo time) and the compensation of concomitant signal modulation (T2star and B1+/B1- from transmit-receive coil) allows for a single slice to be mapped within 5min at a resolution of 2x2x10 mm^3. Reference sodium concentration vials attached to the coil serve as calibration of the sodium MRI signal.

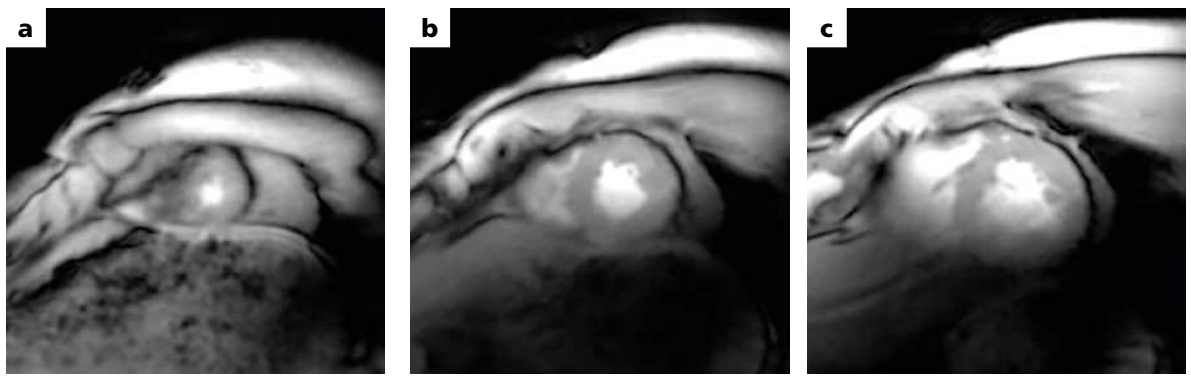
Figure 1: Top-left is B1+/B1- map, Top-right is T2star map, Bottom-left is anatomical MRI image of the heart using conventional 1H-MRI, and bottom-left is the map of long-relaxation sodium concentration after corrections of the sodium MRI signal using the maps at the top.

Figure 2: Overlay of long-relaxation sodium map onto the anatomical MRI.

High-resolution Simultaneous Multi-Slice (SMS) dynamic MRI of the heart at 7-Tesla

Increased signal-to-noise ratio from the 7-Tesla MRI is harnessed for refined imaging of heart. Simultaneous Multi-Slice (SMS) cardiac dynamic MRI (cine) permits the acquisition of three thin-slices (4 mm) within a 10 s breath-hold. Robustness to patients motion and limited breath-hold capacity is guaranteed through a dedicated self-calibrated SMS technique tailored for cardiac imaging. Morphologic and dynamic information of the myocardium is achieved with millimetric resolution (0.9x0.9 mm^2). Strong intensity variations characteristic of 7-Tesla MRI can be observed from anterior to posterior myocardial segments.

Figure 3: SMS cine acquired within 10s showing diastole (relaxed phase of the cardiac cycle) of the apex (a) mid-ventricular (b) and base (c) slices.



Morphologic and dynamic information of the myocardium is achieved with millimetric resolution (0.9x0.9 mm^2). Strong intensity variations characteristic of 7-Tesla MRI can be observed from anterior to posterior myocardial segments.

New tools provided by industrial partners and used by cardiovascular surgeons and radiologists are improving treatment of thoracic aorta pathologies.

An increasingly used technique is fusion imaging, in which pre-treatment MR and CT scans of the patient are being fused with angiography images to guide stent-graft navigation through the vascular structures of the patient during the intervention, according to Alexis Jacquier, cardiovascular radiologist at Timone University Hospital in Marseille.

'Fusion imaging enables to lower radiation dose and to reduce the amount of contrast media that are traditionally required in this type of surgery. It avoids having to inject iodine to know where we're at,' he explained.

Covering full aortic pathology management, from diagnosis to care and follow-up

The hospital also hosts the Timone Aortic Centre (CAT in French), a leading regional multidisciplinary centre that covers full aortic pathology management, from diagnosis to patient care and follow-up, with a strong connection with the university. The CAT includes vascular and cardiac surgeons, radiologists, cardiologists, vascular physicians and anaesthesiologists.

The objective is to provide a multidisciplinary approach to provide the best medical care; for instance all thoracic stent-graft procedures are performed by a multidisciplinary team comprised of vascular surgeons, radiologists and anaesthesiologists at CAT.

Imaging has become key in thoracic aorta treatment with the boom of minimally invasive procedures. Besides thoracic disease, Timone Hospital is one of the main centres in France offering endovascular interventional radiology skills to treat patients with carotid and renal disease, which Jacquier and colleague Vincent Vidal perform daily, along with the full suite of cardiovascular interventional radiology procedures – endoprostheses and stent placement, small vessels and tumour embolisation, etc.

Furthermore, the hospital is located close to the medical and biology MR centre (CRMBM), one of the few laboratories in Europe that work with 7-T MRI for diagnostic imaging research.

This proximity enables Jacquier and team to test 7-T methods using sodium instead of proton imaging, a possibility that opens brand new perspectives in heart imaging. 'Sodium electrolytic disorganisation in the myocardium can have an electrical and mechanical impact on heart function.

7-T will enable the development of new applications in the field. It is still a complex task, but we are working hard on different papers on sodium quantification in the myocardium and potential clinical applications' he explained.

Cooperation with cardiologists is essential in myocardial disease management, according to Jacquier, who again stressed the importance of the multidisciplinary approach during patient treatment. 'Patients are now being cared for within the heart team, a model increasingly followed by healthcare facilities in France and beyond,' he explained.

'Whether it's for TAVI procedure, diagnosis or follow-up. Medicine is becoming hyper specialised and mixing profiles and specialties enables us to significantly improve patient care.'

Obligatory three-step training for residents in emergency radiology

Another significant development in France was the reform of the radiology residents' training scheme, which was introduced in 2017. Radiology residents must now undergo a three-step training, including successively: base training (one year), dedicated to emergency radiology; in-depth training (three years), to ensure that every subspecialty in radiology has been covered in their education; and consolidation training (one or two years), providing certification for one or two subspecialties.

The French Council of the Teachers of Radiology (CERF) has been piloting the change for radiology. The French Society of Cardiovascular Radiology now provides e-learning material to ensure homogeneous teaching and training program across the country.

Last September, the series became freely available for French residents on the CERF website, and also available for all radiologists on the website of the French Society of Radiology.

This change is a substantial improvement in the training scheme, because it reflects daily routine better, Jacquier added. 'Cardiac imaging studies are being prescribed every day by all sorts of physicians: GPs, endocrinologists, surgeons, and even oncologists, for instance in pre- and post-chemotherapy evaluation.'

Many things may need updatewing for AI

As for cardiology, the French Society of Cardiology and the French Society of Radiology established a working protocol in 2005; according to this, the cardiologist prescribes the CT and MR scans and radiologist performs the technical assessment and writes the report – and then sends it to the cardiologist. Jacquier: 'This division of tasks promotes the best possible medical care, but everything really depends on the physician's skills. A lot of things may need to be updated as we gradually introduce artificial intelligence.'

Radiologists must also homogenise the way they write the imaging report. Introducing the structured report to exploit data at national level will prove essential for their future.

Another priority is to improve communication not only with patients but also other medical specialties, he said.

The radiologist is no longer alone in a basement reading scans,with no contact

Jacquier will participate in the International Day of Radiology (8 November 2018), an initiative to highlight the radiologist's role in cardiac care.

'Radiology is not a medico-technical specialty, although French administration still classifies us as such. We're a medical discipline. The old-fashioned image of the radiologist reading scans alone in a basement and not having contact with anyone else in a hospital is outdated.

'The radiologist,' he emphasised, 'is now at the centre of patient care and healthcare.' (MR)

Cardiovascular radiologist **Professor Alexis Jacquier**, at Timone University Hospital, Marseille, France, trained in Marseille and Lyon and gained his PhD in San Francisco, USA, supervised by Maythem Saeed and Charles Higgins. In 2006 he integrated the cardiovascular group in the CEMEREM research lab (http://crmbm.univ-amu.fr). He is author and co-author of more than 90 peer-reviewed publications and has presented numerous lectures, tutorials and refresher courses internationally. He also chaired the European Society of Cardiac Radiology membership committee and is current vice president of the French Society of Cardio-Vascular Radiology (Société Française d'Imagerie CardioVasculaire, SFICV).

Today's improved lower leg treatments

Peripheral vascular therapies

Interventional radiotherapy for tibial arteries has increased in recent years. Why? People are getting older and better techniques and materials now permit treatment even of very thin vessels. Professor Dierk Vorwerk, Director of the Institute for Radiology at Ingolstadt Hospital, where almost a third of all interventions in his department are performed on the lower leg, described the most important innovations.

Interview: Daniela Zimmermann

Blood vessels in the lower leg form a fine structure in the upper range of three millimetres and lower range no more than 1.5mm. With the wires and balloon catheters available in the past only limited interventions were possible. Meanwhile the wires and instruments are more delicate and above all more versatile. Thus, in addition to balloon catheters that are up to 20 cm long today, there are so-called support catheters. They are tapered at the tip, very stable, and support the process of pushing by expanding the vessel in front. The stability can also be improved by use of additional guide catheters or sluices.

New on the market are also atherectomy systems that work like a milling machine, removing the plaque from the walls of the vessels and pulverising it. With new materials come new methods. If access cannot be obtained through the groin, then the vessel is punctured exactly behind the stenosis in the tibia and then opened from there in reverse. That also functions through the foot arch.

'We call this rendezvous technique when the access is sought equally from above and below,' Vorwerk explained. However, these special techniques are more of an exception in his department. 'The work from the ipsilateral groin usually works well, so I can dispense with special techniques.' Installing catheters in a crossover procedure is another matter. In this case work begins from the opposite side, a disadvantage since, due to the longer distance and loss of energy in the aortal bifurcation, it is not possible to use full force. Access from below can be chosen as an alternative.

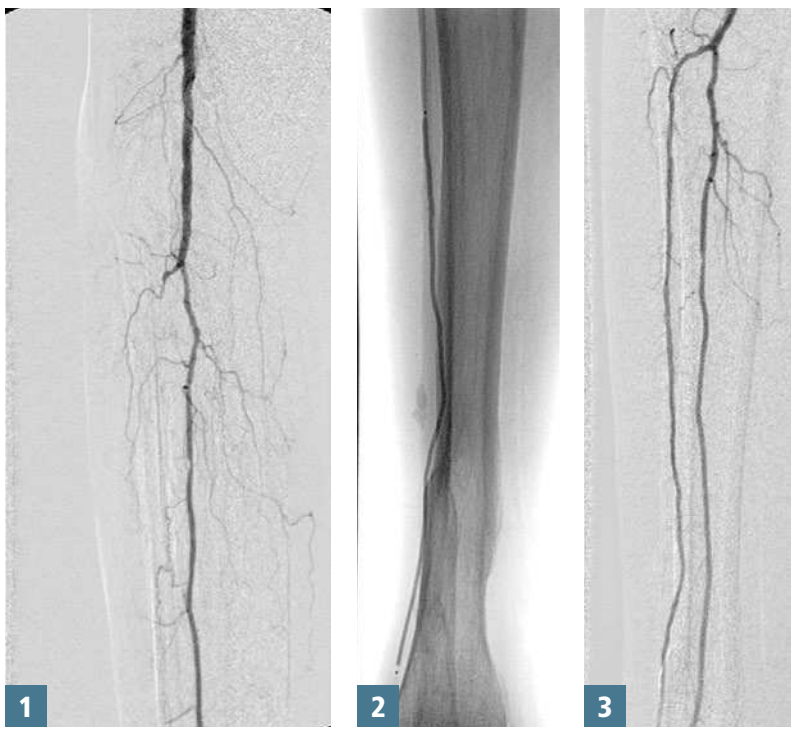
Where is the intervention?

Along with the anterior and posterior arteries, there is the arteria fibularis deep in the middle. For most patients this is the most important vessel, since its strong collateral supplies blood to the foot—even when nothing else helps any more. In addition, the vessels below the ankle are dilated and not even with very bad results, although the data situation is rather thin. The knee artery is the main line for blood supply to the lower leg. It often exhibits heavy calcification, leading to restrictions in the foot.

However, a stent implantation at the level of the joint line is disadvantageous. The collaterals from the deep femoral arteries that end above and below the knee are important for supplying the leg and can partially compensate for constrictions in the knee artery.

The time for treatment?

The peripheral vascular illnesses are described according to the Fontaine or Rutherford classification. The serious stages lead to static pains (Fontaine III, Rutherford 4) or trophic disorders; often accompanied by open wounds, black toes and similar symptoms (Fontaine IV, Rutherford 5-6). 'We treat the lower leg arteries starting with stage III, that is with the incidence of static pain or trophic disorders.' The only exception: if patients have an isolated narrow stenosis of truncus tibiofibularis causing calf pains when walking then Vorwerk intervenes earlier.



1: Complete closure of the A. tib. ant. with the exception of a small stub at the outlet
2: After passage with a 0.014 in lead wire PTA with a 200 mm-long PTA balloon and 3 mm diameter
3: Subsequent reopening of the artery along its entire length

The main objective: wound healing

A decisive criterion for an intervention's clinical success is the functioning of the small arterioles. There are patients for whom the vessel can be opened very well but without any improvement in the blood supply to the tissue. The reason is that the small vessels are no longer able to transport the increased blood volume to the tissue that is sent to the foot. Frequently this cannot be judged in advance. There is current work being done on tests for more certain prognoses.

Interventions in the tibial arteries are not intended primarily to keep the vessel open for the long-term. Rather, precedence is given to healing the wound on the foot and returning the patient to a stable stage 2b. 'Wound healing, and thus conservation of the foot and lower leg tissue, that is to say avoiding amputation, is the main issue – naturally with the diabetic foot, but not only there. Compared to that, elimination of patient pain while walking is rather secondary.' After all, most of these patients no longer walk very much and, as diabetics, also no longer have any pronounced sensitivity to pain.

Percutaneous balloon catheterisation before bypass and stents

In the context of the vascular conference, angiologists, cardiologists, nephrologists and radiologists clarify the responsibilities and discuss the planned intervention. 'Usually we prefer a percutaneous balloon first. If that does not work, then a bypass is set. We have become more cautious here however since once set a new opening is often difficult. In addition, the consistency results are not optimal. The last resort with a blocked vessel is also the very controversial sympathicolysis. Here the sympathetic nerve network in the back is destroyed to force a widening of the vessels.

Stents do not play much of a role in the lower leg: the lesions are sometimes more than 20 cm long and stents of this size are rare.

No reimbursement for drug-eluting balloons

The use of drug-eluting balloons is currently in dispute. The initial findings of a large-scale study have been really convincing. The procedure also suffers from the fact that a health insurer does not absorb the costs. Additionally, a meta-analysis has shown that the mortality rate for patients treated with coated balloons was higher than those without drugs: 'Although the difference was very small, it was still significant.'

These uncertainties have meant that drug-eluting balloons are only used if the patient explicitly consents after thorough explanation.

Possible candidates for a repeat intervention with a drug-eluting balloon, despite the risk are patients exhibiting a new constriction after only three months, or who have developed a pronounced neointimal hyperplasia in a stent.

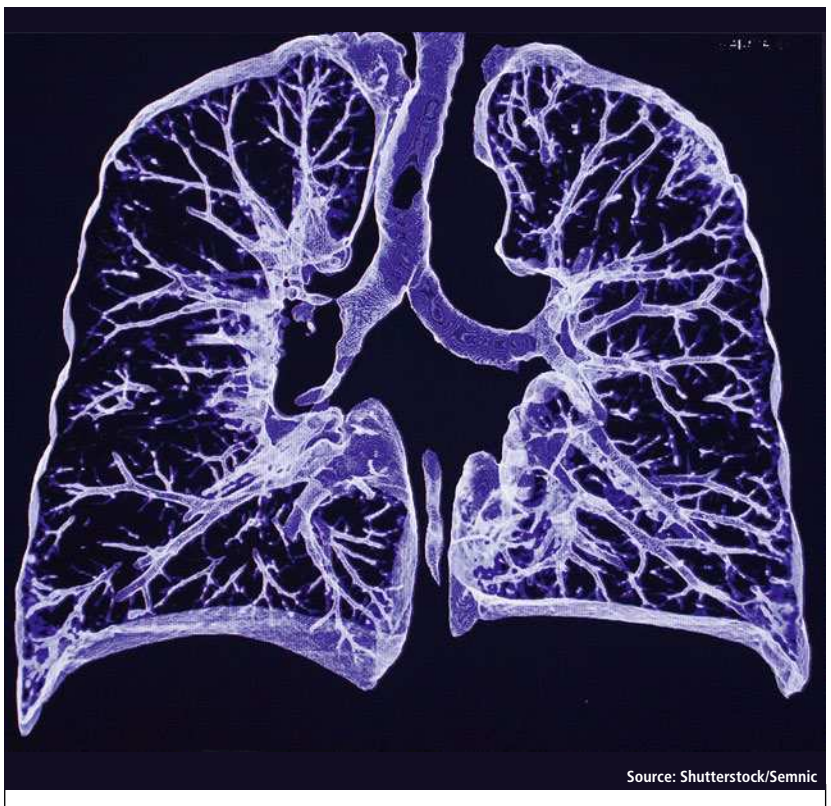
Professor Dierk Vorwerk, co-founder (in 2008) of the German Society for Interventional Radiology and Minimal Invasive Therapy (DeGIR) has directed the Institute for Diagnostic and Interventional Radiology at the Klinikum Ingolstadt for 21 years. He is a renowned author of numerous scientific papers and book contributions and is a member and honorary member of many national and international specialty societies. He has also chaired the DeGIR (2012-2014) and was President of the German Röntgen Society (2015-2017).

The only chance of a lung cancer cure is early diagnosis

Can we afford not to offer lung screening?

For lung cancer patients life expectancy has hardly improved since 1970. A ten-year survival is 5%, making this the leading cause of death among all cancers. One reason is that, in most cases, the disease is diagnosed far too late.

Interview: Daniela Zimmermann



Source: Shutterstock/Semnic

Previous evidence on the benefits of screening programmes to detect lung cancer early, was mainly based on data from the NLST study in the US (National Lung Screening Trial; N Engl J Med 2011), was considered insufficient. However, the publication of the Belgian-Dutch NELSON study (De Koning et. al, 2018) has just changed this. For the first time, lung cancer screening has moved within reach.

Professor Mathias Prokop, head of the Department of Radiology at Radboud University Hospital Nijmegen is among leading advocates of low-dose CT screening for lung cancer for high risk patients. At this year's congress he explained aspects of the current debate in the context of the Holzknecht Lecture.

Considering present evaluation by the Federal Office for Radiation Protection (BfS) as to whether lung screening makes sense, what might be the main concerns?

'First, the BfS obviously deals with radiation protection. As a result of new technology, radiation exposure during chest CTs now poses an almost negligible risk,' Prokop explained. 'In the NLST study, the dose per examination was between one and three mSv; in the NELSON study it was lower than one mSv. Some experts even say that they can screen with 0.2 - 0.1 mSv.

'What the current evaluation procedure is really about is the assessment of the risk/benefit ratio, given false positives and over- diagnosis and treatment. There is a danger that patients who would never have died of lung cancer are exposed to the potential complications of an invasive medical procedure. If there is no need to intervene it should not be done.'

What is the false positive rate?

'It depends what you define as positive. The NLST study classed all nodules larger than 4mm as positive, which leads to an extremely high false positive rate of 96.4%. Those who carried out the study simply lacked empirical values because they were the first to analyse this. In all later trials, results were only classed as positive where further examinations were carried out because lung cancer was explicitly suspected.

'Therefore, the false positive rate for the NELSON study was only 10-15%, depending on which screening round you looked at. There are now new suggestions as to how the false positive test results can be pushed below five percent. Then definitely this would be acceptable and considerably better than the results achieved in breast cancer screening.'

How does the radiologist detect lung cancer on a CT scan?

'There are basically two methods that help us. There is morphology, where the size or the volume of a suspicious region plays the most important part.

'Then there are other morphological criteria that help with tumour determination, such as the shape or the localisation. A biopsy is only recommended for patients with large, high-risk pulmonary nodules. All other patients just receive follow-up examinations. This is where the second category comes into play: changes over time.

The rate of growth is significant in terms of mortality

'If the pulmonary nodule grows very fast, it is most likely to be a malignant tumour; if it grows slowly, it is likely to be either a benign tumour or a malignant tumour which the patient will live with until their death (from causes other than lung cancer).

'We must not forget that many patients who are recruited for lung screening are already multimorbid, because of their age and additionally they may, for instance, be at higher risk of a heart attack or a stroke.'

Would you say that lung screening helps to save lives?

'Well, it depends how you define saving lives. If you mean that patients do not die from lung cancer, then yes. The NELSON study showed that mortality among men decreased by 26% and among women even by 61%. Lung cancer screening appears to work better among female patients. This is probably because comorbidity amongst women is lower, and they more frequently have slow-growing tumours.

'What is important is that, if we screen for long enough, the optimum effect on survival will develop. First data from the German LUSI (Lung Tumour Screening and Intervention Trial) confirms that the advanced tumour stages only disappear from about the third round of screening. It just takes a while until all tumours within the population have been captured and for new tumours to have been detected early enough.

Weighing up the costs of life-extending therpies

'Can we afford not to offer screening? Although life-extending treatment procedures for advanced tumour stages, such as immunotherapy, work well, they are also very expensive and a significant burden for the healthcare system. The cost per life saved by a screening programme is therefore much lower. The only chance of a cure is to diagnose lung cancer as early as possible.'

Radiology **Professor Mathias Prokop** heads the Department of Radiology and Nuclear Medicine at Radboud University Nijmegen, in the Netherlands. Over the last decade he has extensively researched chest screening with CT and he was significantly involved in the Dutch-Belgian lung cancer screening study (NELSON). He has been vice chairman of the Dutch Radiology Society and has repeatedly received awards from the Radiological Society of North America and the German Radiological Society.

The search for new MRI contrast a

Aiming to work without radioa

MRI is now indispensable for diagnosing diseases and monitoring therapies. However, the ongoing discussion on gadolinium deposits in the brain has intensified the search for alternatives. Dr Daniel Paech of the German Cancer Research Centre in Heidelberg, Germany, discussed potential solutions to acquire high-quality images without contrast agents.

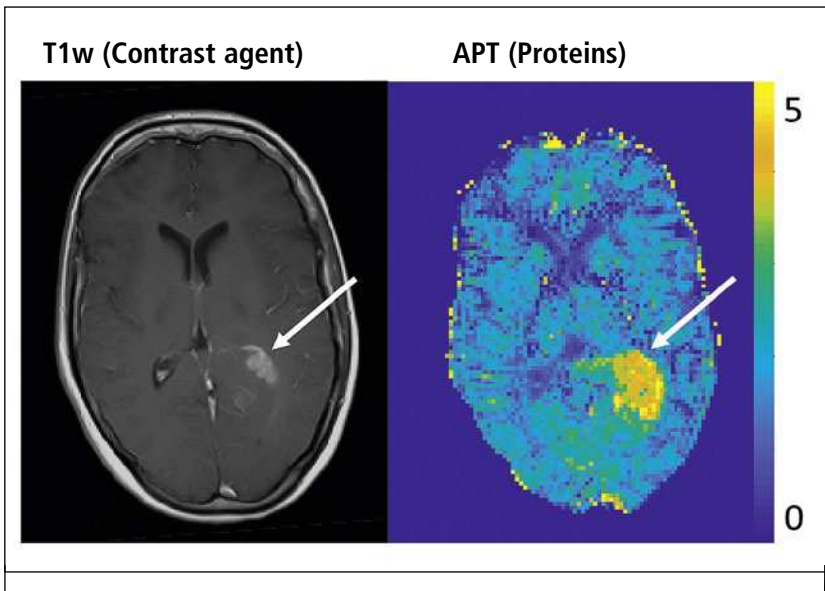
Interview: Sascha Keutel

Dr Paech, you found a way to detect brain tumours using glucose. Could you describe your method?

'Conventional MRI measures proton signals in water. Since about 60 percent of our body consists of water, a clear image can be generated. Contrast agents intensify the signals in the vessels and between the cells, albeit they do not enter the cells themselves. Glucose on the other hand is taken up by the cells and metabolised. Tumour cells need sugar to meet their high energy demand.

'To visualise the much lower levels of glucose, my colleagues Patrick Schünke and Moritz Zaiss from the Division of Medical Physics in Radiology and I have developed a method to selectively intensify the glucose signal. It's based on the physical process of magnetisation transfer, which means the signal of the glucose protons is transferred to the body water measured during the MRI procedure. This effect is proportional to the local glucose level and thus maps the regional change in the glucose level.

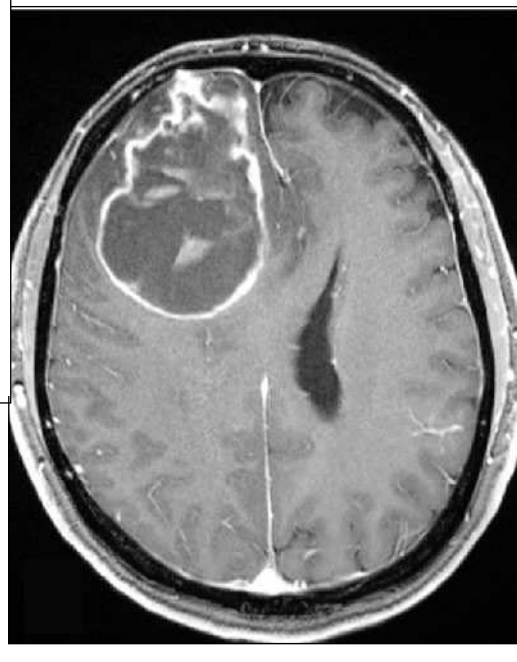
'After completion of the initial technical developments, we conducted a proof-of-concept study with a group of ten glioblastoma patients. In this study, we could confirm increased glucose signals in the tumours.'



Left: conventional morphological contrast-enhanced image of a brain tumour at 3 Tesla; Right: contrast-free protein measurement at 7 Tesla.
© D. Paech/DKFZ

PET has long been used to visualise sugar metabolism in tumours. How does your method differ from those techniques?

'PET uses radioactively marked glucose molecules. We work without radioactivity, which means there is zero radiation exposure for the patient. However, there is one difference to radioactive tracers: we don't know yet whether our images contain metabolism information or, as in conventional



Breast cancer treatments

Simply monitoring might be best

Breast cancer screening is a well-designed and scientifically proven, evidence-based procedure, but has pitfalls such as under-detection and over-diagnosis. Surgery or radiotherapy may have serious consequences on health and must therefore be administered in carefully selected patients. Research is ongoing as to how screening can help differentiate between the cancers that deserve treatment from those that don't, a British expert told delegates during ECR 2019.

Report: Mélisande Rouger

Screening is effective and helps save millions of patients with breast cancer (BC) annually – but it is not without flaws, and can trigger a chain of actions that may cause more harm than doing nothing. In some cases, it might be best to monitor the disease than to treat it right away, according to Matthew Wallis, a breast screening radiologist and researcher in Cambridge, United Kingdom.

Source: Shutterstock/GagliardiPhotography

Treatment has side effects

Treatment is not risk free, Wallis explained. 'I've been working in breast screening for rather more years than I wish to remember and I firmly believe I've done more good than harm. But, there are probably women out there who have received more treatment than was strictly necessary and probably have had harm as a result of my interference, and not just the bruises I cause when I do vacuum biopsies, 'he said.

Cancer is a very complicated process and personalised care is much more than just the oncologist prescribing more and more expensive drugs for fewer and fewer people but very targeted. 'It is also reducing what radiologists do at the lower end scan,' Wallis said.

Cancer is highly complex and requires different approaches depending on the patient and her disease. 'With breast cancer, we're still very fixated on this multistep progression based on epidemiology and morphology and it's been a very good thing. Actually the molecular and genetic basis of this is much more complicated,' he said.

Long treated as a single disease process, the medical community is shifting away from that. 'Treatment has changed: we've moved from appalling surgery to mastectomy, to partial mastectomy, to local mastectomy, to radiotherapy and chemotherapy. In the UK, some women are not even offered treatment at all for their axilla. We used to rip everything out, then a little out, and now there's nothing,' he said.

Knowing when and when not to treat could reduce side effects of current treatment, which range from death from catastrophic sepsis to lymphoedema, chronic pain and musculoskeletal symptoms. Avoiding treatment when unnecessary would also spare women burdening cosmetic and psychosocial consequences that may drastically impact on their health and quality of life.

BC screening still falls short in distinguishing between cancers that should or should not be treated, i.e. differentiating low risk from high-risk cancers. 'We pick them all up. That's because our targets for screening are about cancer detection and not about detecting killing cancers,' Wallis explained. 'Matching high-risk disease biology with chemotherapy is now possible, but it's still tricky to identify biologically low risk cancers and that probably wouldn't need the full game of treatment like chemo, radiation therapy and surgery. Since those cancers probably would not develop or kill anyone in their normal life expectancy.'

Differentiating low and high-risk cancers is -improving

Low risk DCIS can now be spotted early with mammography and confirmed by biopsy; it might never become cancer and if it does, it would do so much later on in life. It might be more interesting to offer active monitoring than immediate treatment for these conditions, according to Wallis. 'The risk of these DCIS is so low that some people would like to reclassify them as indolent breast lesions or idle lesions, rather than calling them cancer. DCIS can be detected with imaging potentially 10 to 15 years before they present clinically, which would leave plenty of time to assess if a lesion turned cancerous or not,' he pointed out.

Other low risk cancers exist and need consideration, as they could benefit from active monitoring, i.e. by performing mammography once a year.

Three international randomised controlled trials are currently looking specifically at active monitoring vs. surgery for low risk DCIS: the LORIS (The LOw RISk DCIS trial), LORD (LOw Risk DCIS) and COMET (Comparison of Operative versus Medical Endocrine Therapy for Low Risk DCIS) trials, each with a 900-patient cohort.

In the UK, the PRIMETIME trial will tackle invasive cancers that can potentially spread over the breast. 'We're offering women aged over 60 with small, low risk cancers to opt in to radiotherapy or opt out, with the anticipation that radiotherapy is unlikely to offer them any benefit,' Wallis said.

The SMALL trial, also in the UK, will follow 850 women aged over 60 with tiny low-grade invasive cancers over five years, after offering them the opportunity to be treated with vacuum biopsy and subsequent radiotherapy, vs. surgery and radiotherapy.

'It's about avoiding unnecessary treatment. Should we re label these cancers? I don't know,' he said. 'I'm not sure just changing the box to include more or less is necessarily a good idea.

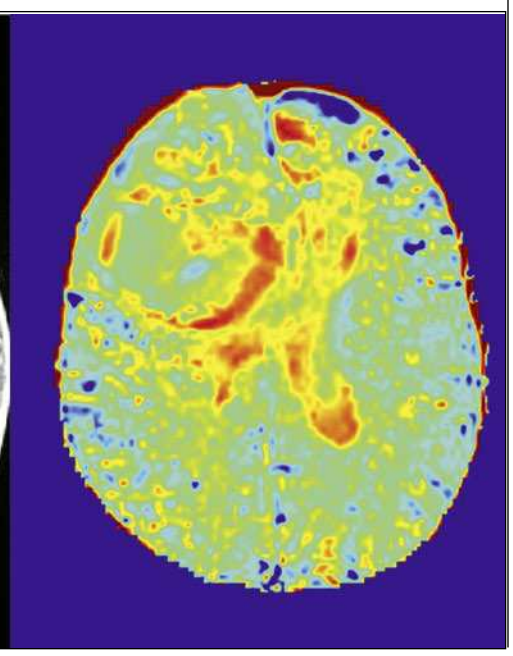
'We need to be out there explaining these women that cancer is an enormous great house of lots of different things and some are bad news and some are good news. And if it's good news, you can live with it in symbiosis and we'll follow you and if it gets worse,' Wallis concluded. 'We'll sort you out and your survival will still be the same.'

Mathew Wallis has been a breast screening radiologist since 1989. After 19 years as director of breast screening in Coventry, Warwickshire and Solihull, he moved to Cambridge to concentrate on research – with a major research interest in using routinely collected data to optimise all aspects of breast screening from the imaging chain to surgical management. His other interest is DCIS and de-escalation of treatment. He is also chief investigator of LORIS, the Low Risk DCIS trial.

gents

ctivity

MR images, only perfusion of tumour tissue and normal vessels. Thus, it's very possible that we only see increased tumour perfusion, but not increased metabolic activity. At this point we are doing basic research which does not compete with PET procedures, but which is a discrete method.'



Left: brain tumour in conventional contrast-enhanced MRI; Right: glucose MRI at 7-Tesla.

In a different study you conducted protein measurements in brain tumours. What were the results?

'Our objective was the development of contrast-free 7-Tesla MRI and isolation of specific protein signals. In native sequences, we examined glioma patients to find out whether there is a correlation with histopathology parameters such as IDH mutation status or MGMT promotor methylation status. We were indeed able to confirm strong correlation with IDH mutation status. Just like our glucose MRI project, this approach uses a chemical transfer effect between proteins and the water in the tissue, the so-called chemical exchange saturation transfer – CEST.

'Furthermore, we wanted to find out whether this protein signal correlates in some way, shape or form with the therapy response and patient survival, that is prognosis.

'We found an inverse correlation of progression-free survival and overall survival of glioma patients with the protein signal. This means when the tumour shows a very high percentage of protein, patient prognosis is poorer. Thus, the protein signal seems to indicate tumour aggressiveness.

'In a next step, we plan to check whether these results also apply to other tumours or organs, in particular breast and prostate cancer, because these tumours have a much higher incidence than brain tumours and are thus even more relevant to society at large.

'We also want to find out whether these protein measurements can be conducted with less powerful MRI scanners. Currently, these techniques can only be performed at 7 Tesla because the metabolite level is low and the measured effects are small. We profit from the strong magnetic field of the 7-Tesla scanner. We aim to transfer the method to 3-Tesla MR systems to make it more widely available. However, at this point it's entirely unclear whether these low levels can be reliably measured at 3 Tesla.'

What other new MRI contrast agents are you working on?

'We want to find MRI contrast agents that provide information that's not included in the currently available sequences, in order to contribute to a permanent improvement of patient care. X nuclei MR imaging is particularly promising. Normally, MRI measures the magnetic moment of the hydrogen nuclei linked to the spin. However, X core MRI measures the magnetic moment of other nuclei, such as the sodium nucleus, or certain oxygen isotopes that provide other physiological information. A conventional MRI scan does not yield this information because the level of these substances in the body in relation to the water is much, much lower. That means we need high-field strength.'

Dr Daniel Paech MD MSc is resident physician and researcher in diagnostic radiology at the German Cancer Research Centre in Heidelberg (DKFZ). He gained his physics diploma in 2011 and, in 2015, his medical degree exam at the University of Karlsruhe, Heidelberg and the Sorbonne in Paris. He is medical director of 7 Tesla MRI in Professor Heinz-Peter Schlemmer's radiology department at the German Cancer Research Centre, Heidelberg.

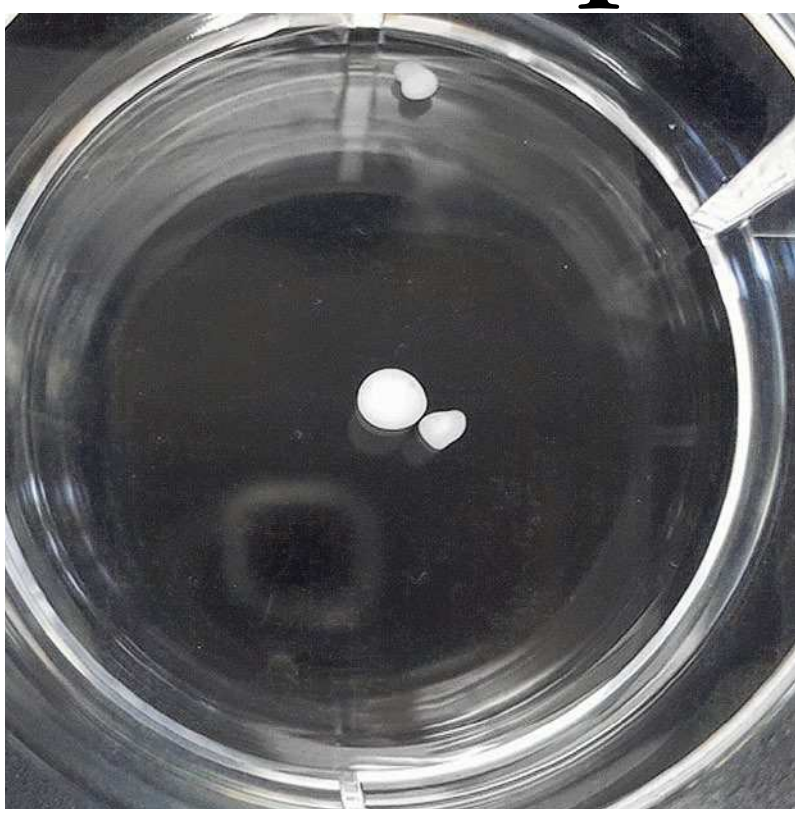
R research on treatment response – growing brain tumours in the petri dish

3-D organoids for glioblastoma patients

Report: Brigitte Dinkloh

Research that might lead to new treatment options and longer survival for patients with glioblastoma – a malignant and particularly invasive type of brain tumour – is ongoing at ZHT, the Centre for Brain Tumours, and the Wilhelm Sander Neuro-oncology Treatment Unit at University Hospital Regensburg, which form one of the largest and most modern facilities for brain tumour treatment in Germany.

The hospital's head of neuropathology, Professor Markus Riemenschneider, is a key member of the interdisciplinary clinical and research team, who studies the in vitro growth of glioblastoma tumour cells which behave like tumour cells in the human body. 'These tumour organoids offer new insights into tumour growth. One day, we might even be able to translate this approach to personalised medicine and test for individual treatment response,' Riemenschneider explained.



Tumour organoids in the Petri dish

Maintaining variety in the cells

The Centre for Brain Tumours researchers have long been interested in molecular changes in cells. To start a cell culture, they use tissue samples that were isolated during surgery (with prior patient's consent). Previously, this method had a major drawback: the cell heterogeneity could not be maintained – all cells were 'harmonised'. 'A typical feature of glioblastoma is cell heterogeneity,' Riemenschneider pointed out. 'There are different types of cells in a tumour, some are hypoxic, others are normoxic; that is, they differ in terms of oxygen concentration. Furthermore, you will see necrotic as well as perfused tissue areas. This variety of active tumour cells means a variety of genetic programs are running. When we isolate these cells and turn them into a cell culture, we only have one of these conditions – the variety is lost.'

The new 3-D organoid models can overcome this hurdle. Currently, there are few studies on this issue – and these mostly on gastrointestinal and colorectal tumours. However, these models are crucial for glioblastoma research since all cells grow, interact and assume different functions – just like in a real tumour. 'We use an extracellular matrix which provides a surface for these cells to dock on. The matrix is metabolised after a while, but the cells retain their structure and integrity. This is promising because it might enable us to model the actual patient situation more realistically: when we can map the gradients, for example regarding oxygen saturation and nutrient supply, we will be able to see much more than in a normal cell culture,' the neuropathologist added.

Producing a brain

Tumour organoids are limited neither by species barriers nor artefacts – two obstacles in research that uses tumour cells implanted in mouse brains. Moreover, interindividual barriers don't exist in a purely autologous system. The researchers, who cooperate with colleagues at the University of Erlangen, are not only able to produce tumour organoids in a Petri dish; they can even produce miniature brains, using a procedure which received the 2012 Nobel Prize for medicine: all cells of the human body can be produced from healthy cells via induced pluripotent stem cells.

'This procedure,' said Riemenschneider, 'opens up entirely new options to confront cultured patient tumour cells with own miniature brains. This allows us to observe tumour cells' growth onto and into the brain cells – this is what, de facto, determines healthy and pathological cells. In the long run, we hope to develop treatment options.'

The research project is still in an early phase, but the goal is a standardised procedure that tests treatment response and effectiveness on the individual patient level.

Insights may come into rare brain tumours

In turn, this might yield insights relevant to the treatment of rare brain tumours that are difficult to assess in conventional cell cultures. Since there are more than 100 types of brain tumours, a highly differentiated approach is needed.

The Wilhelm Sander Treatment Unit appears to be heading in the right direction as shown in the enhanced patient survival rate recorded since the facility was set up. Whilst overall glioblastoma prognosis remains poor, at the centre we could significantly prolong average survival rates.

Dr Markus Riemenschneider, a University Professor and Head of Neuropathology at the University Hospital Regensburg since 2010, received his medical training as well as specialist training in neuropathology at the University of Düsseldorf. A Mildred Scheel Scholarship of the Deutsche Krebshilfe Foundation enabled him to become a researcher in the Department of Pathology at the Massachusetts General Hospital and Harvard Medical School, Boston, USA. In 2008, he completed his specialist physician training in neuropathology and headed the independent Max-Eder Junior Working Group of the Deutsche Krebshilfe in Düsseldorf until his present appointment in Regensburg.

Riemenschneider has received a number of awards for molecular neuro-oncology research, and was, inter alia, appointed a member of the Junge Kolleg (Young Scholars Group) of the North Rhine-Westphalian Academy of Sciences, Humanities and the Arts. In 2011, he received the Sibylle Assmus Award for neuro-oncology. Another focus of the professor's work is quality control in neuropathology. He is an expert for DAkkS – the national accreditation body for the Federal Republic of Germany – and a member of the Scientific Board of QuIP GmbH – Quality Assurance Pathology Initiative GmbH, in Berlin.

'We aim to ensure a longer good quality life for our patients,' Riemenschneider stressed.

With his Regensburg team, he has taken the first successful steps towards this goal: two to three months post-surgery tumour organoid cultures are available for certain patients. These can be used to test treatment response in the lab should a tumour return.

EUROPEAN HOSPITAL
European Hospital Verlags GmbH
Theodor-Althoff-Str. 45,
45133 Essen, Germany
Phone: +49 (0)201 87 126 850
Fax: +49 (0)201 87 126 864
E-mail: info@european-hospital.com
www.healthcare-in-europe.com

Editor-in-Chief: Brenda Marsh

Editorial team:
Wolfgang Behrends, Sonja Buske

Senior Writer: John Brosky

Executive Director:
Daniela Zimmermann

Founded by Heinz-Jürgen Witzke

ISSN 0942-9085

Correspondents

Austria: Michael Krassnitzer, Christian Pruszinsky.

China: Nat Whitney

France: Jane MacDougall

Germany: Anja Behringer, Annette Bus, Walter Depner, Cornelia Wels-Maug, Holger Zorn

Great Britain: Brenda Marsh, Mark Nicholls.

Malta: Moira Mizzi

Spain: Mélisande Rouger, Eduardo de la Sota

The Netherlands: Madeleine van de Wouw.

USA: Cynthia E. Keen, i.t. Communications, Lisa Chamoff

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

Subscription rate
6 issues: 42 Euro, Single copy: 7 Euro.
Send order and cheque to:
European Hospital Subscription Dept

Printed by: WVD, Möhrfelden, Germany

Publication frequency: bi-monthly

Representatives

China & Hongkong: Gavin Hua, Sun China Media Co, Ltd.
Phone: +86-0755-81 324 036
E-Mail: 627416876@qq.com

Germany, Austria, Switzerland:
Ralf Mateblowski
Phone: +49 6735 912 993
E-Mail: rm@european-hospital.com

France, Italy, Spain: Eric Jund
Phone: +33 493 58 77 43
E-Mail: jund@european-hospital.com

GB, Scandinavia, BeNeLux:
Simon Kramer
Phone: +31 180 6200 20
E-Mail: kramer@european-hospital.com

Israel: Hannah Wizer, International Media Dep. of El-Ron Adv. & PR Co., Ltd.,
Phone: +972-3-6 955 367
E-Mail: ronin@netvision.net.il

South Korea: Jane Park, MCI
Phone: +82 2 730 1234
E-Mail: mci@unitel.co.kr

Taiwan: Charles Yang,
Phone: +886 4 232 236 33
E-Mail: medianet@ms13.hinet.net

USA & Canada:
Hanna Politis, Media International
Phone: +1 301 869 66 10
E-Mail: hanna@media-intl.com

Positive findings in PD-1 inhibitor immunotherapy

Hope increases for HIV cancer patients

Jean-Philippe Spano MD PhD heads the Medical Oncology Department at the Pitié-Salpétrière-Charles Foix Hospital Group in Paris, France. As well as practising medicine, he is a university professor and member of INSERM research group (UMRS1136) at Sorbonne University, dedicated to the epidemiology of HIV and its treatment, in France. In addition to his involvement with CANCERVIH, he is honorary president and current committee member of the Association for Teaching and Research for Oncology Interns in France (AERIO) and a board member of the American Association for Cancer Research (AACR).

Report: Jane MacDougall

Advances in antiretroviral therapy mean that today, people infected with the human immunodeficiency virus (HIV) can expect a healthy and long life. However, living with HIV does increase the risk of cancer. The reasons for this are multiple and include behavioural risk factors (smoking etc.) but many cancers can be attributed to the effects the virus has on the immune system, specifically its action of reducing the CD4+ cell count.

CD4+ cells are fundamental to fending off both infections and also the early stages of some forms of cancer. Co-infection with other viruses is common in chronic HIV infection and is often with viruses that have known oncogenic effects. Both the HPV (human papilloma virus) and HCV (hepatitis C virus) have been linked to the development of cancer in HIV-positive individuals as they age. While the incidence varies depending on the type of cancer, in general someone who is HIV positive has a two to three times higher risk of developing cancer during their lifetime than someone who is not infected.

Improving the treatment of HIV-positive cancer patients

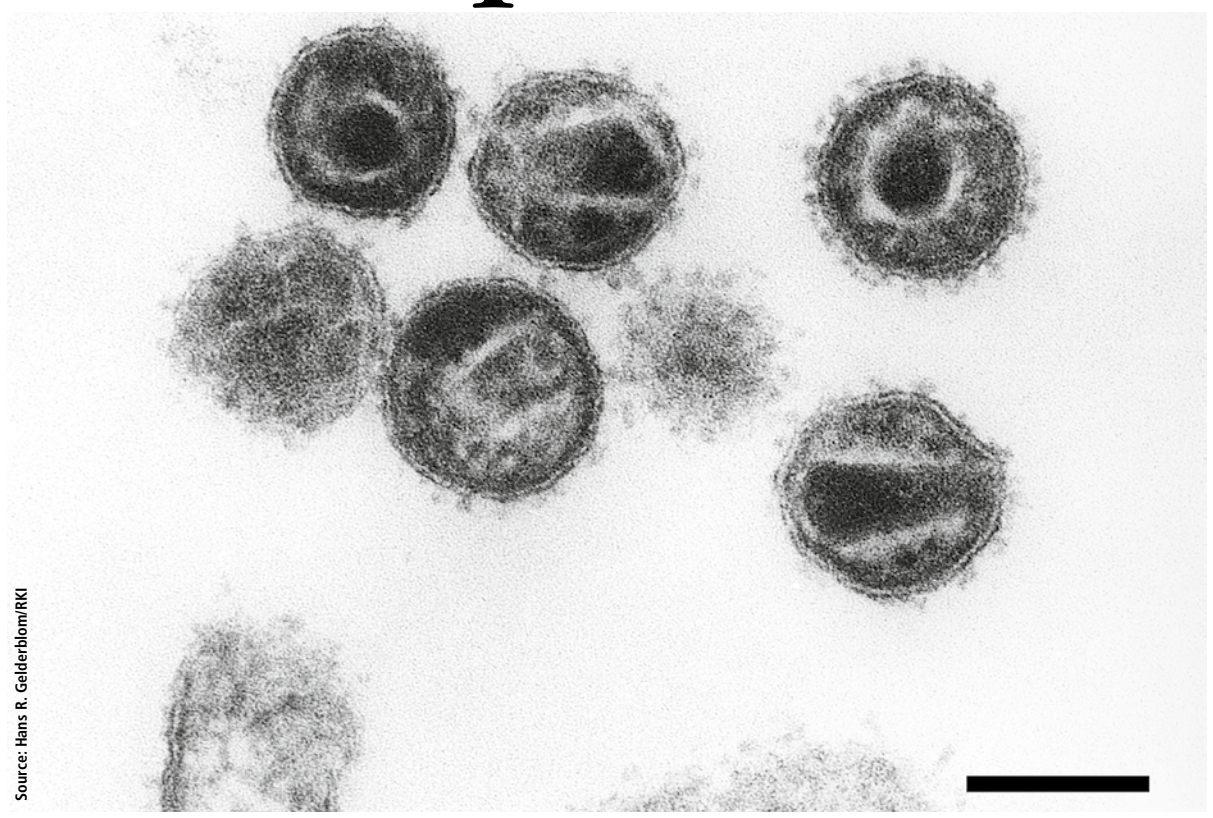
For a long time, classical cancer treatments, such as radiation and chemotherapy, both with known immunosuppressive properties, were used at lower intensity in HIV-positive cancers than to treat a similar cancer in an HIV-negative individual.

French oncologist Professor Jean-Philippe Spano, coordinates CANCERVIH, a nationwide network of expert centres working together to improve the treatment of HIV-positive cancer patients. Created in 2014, and financed by the national Institute of Cancer (INCa), the network aims to optimise cancer management for people living with HIV, which includes treating them as the general population. Unusual in its aims, the network's objective is to treat two chronic illnesses simultaneously, cancer and HIV.

The experts meet every 15 days to discuss progress and treatment of their patients (670 followed by the network since its inception). The expertise within the network includes oncology, haematology, infectiology, virology immunology, pharmacology, etc. with each of the network's regions coordinated by a duo of regional specialists, one in HIV, one in cancer. The centres are mainly public hospitals or cancer centres. Antiretroviral therapy should be continued throughout cancer treatment and CD4 counts and HIV viral load should be closely monitored.

Immunotherapy: a breakthrough in cancer treatment

Among recent breakthroughs in cancer treatment, particularly lung cancer, has been the introduction of immunotherapy, with monoclonal antibodies, or biologics. These treatments harness the power of the body's immune system to destroy the cancer cells. Since their introduction, many advanced-stage lung cancer patients have experienced long-lasting remission and prolonged survival rates.



Source: Hans R. Gelderblom/RKI

Several so-called 'checkpoint inhibitors' are approved for use in France. Amongst these are the PD-1 (Programmed cell death protein 1) inhibitors nivolumab and pembrolizumab. PD-1 is present on the surface of T cells, including CD4+. By binding to its ligand, PD-L1, expressed on a multitude of cells in the body, such as muscle and nerve cells, its actions include the prevention of autoimmune disease by stopping the T cells' recognition of the body's own cells (a checkpoint).

Some cancer cells express large amounts of PD-L1 which, by the mechanism described above, renders them safe from the body's immune defences. Immunotherapy with PD-1 inhibitors therefore prevents PD-1 binding to PD-L1 and allows the cancer cell to be recognised and eventually destroyed by the immune system. While the use of immunotherapy may seem counterintuitive in a population with immunodeficiency, there is some evidence that PD-1 inhibitors in HIV infection may in fact stimulate the immune response and/or facilitate eradication of the virus.

Between May 2014 and January 2019, the CANCERVIH network followed 23 HIV-positive cancer patients treated in routine practice with either nivolumab or pembrolizumab. Of these, 21 had non-small cell lung cancer, one melanoma and one head and neck cancer; all data were collated retrospectively from the CANCERVIH network database.

In his recently published paper (Spano et al. 2019) the professor shows that the efficacy signal for PD-1 treatment (partial response 22%, stable disease 22%) is similar to that in patients without HIV-infection and that these patients tolerated the treatment well with positive impact being reported on CD4+ lymphocyte count and HIV load.

This is the largest, real-life cohort of HIV-positive cancer patients ever to be treated with PD-1 inhibitor immunotherapy. Its positive findings are particularly exciting as they open the way to the inclusion of this population in future trials of new cancer therapies. Thereby creating a more equitable approach to the management of a group of individuals that is often excluded from the latest and best cancer treatments available.

MEDICA

Leading International Trade Fair

DÜSSELDORF, GERMANY
18 – 21 NOVEMBER 2019

www.medica.de

Member of MEDICAAlliance

BE PART OF THE NO.1! **WORLD FORUM FOR MEDICINE**

MEDICA 2019 – Always a heartbeat ahead!

Messe Düsseldorf GmbH
P.O. Box 10 10 06 _ 40001 Düsseldorf _ Germany
Tel. +49 211 4560-01 _ Fax +49 211 4560-668

www.messe-duesseldorf.de

Messe Düsseldorf