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Antimicrobial resistance: reaching out to the UN

Most large pharma companies no longer develop antibiotics

Report: Michael Krassnitzer

A global spotlight has at last highlighted the truly acute problem of antimicrobial resistance. 'At the moment there are lots of political initiatives and a willingness to change,' reports Dr Ursula Theuretzbacher, Head of the Centre for Anti-Infective Agents (CEFAIA) in Vienna, one of the organisers of the Congress of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and the American Society for Microbiology (ASM), held in the Austrian capital (21-23 September: 'Drug Development to Meet the Challenge of Antimicrobial Resistance').

Simultaneously (21 September) a high level meeting on the subject of antimicrobial resistance was held in New York during the United Nations General Assembly. 'This was only the fourth time in the history of the United Nations that a health issue was discussed on this level,' Theuretzbacher emphasises. Decision makers have now heard what doctors have repeatedly warned – that they will increasingly face situations where they have no treatment options left, and where patients will be at higher risk of dying from infections.

Theuretzbacher has encountered the political will to introduce measures against the spreading antimicrobial resistance in many countries. 'Only a whole package of measures will provide a remedy,' emphasises the CEFAIA leader. This includes infection control, antimicrobial stewardship, i.e. the selective use of antibiotics in those cases where

this is actually necessary, the expansion, or creation respectively, of surveillance systems recording the impact of resistance in the individual countries, the reduction of the use of antibiotics in animal breeding, the avoidance of environmental pollution – and the development of new antibiotics.

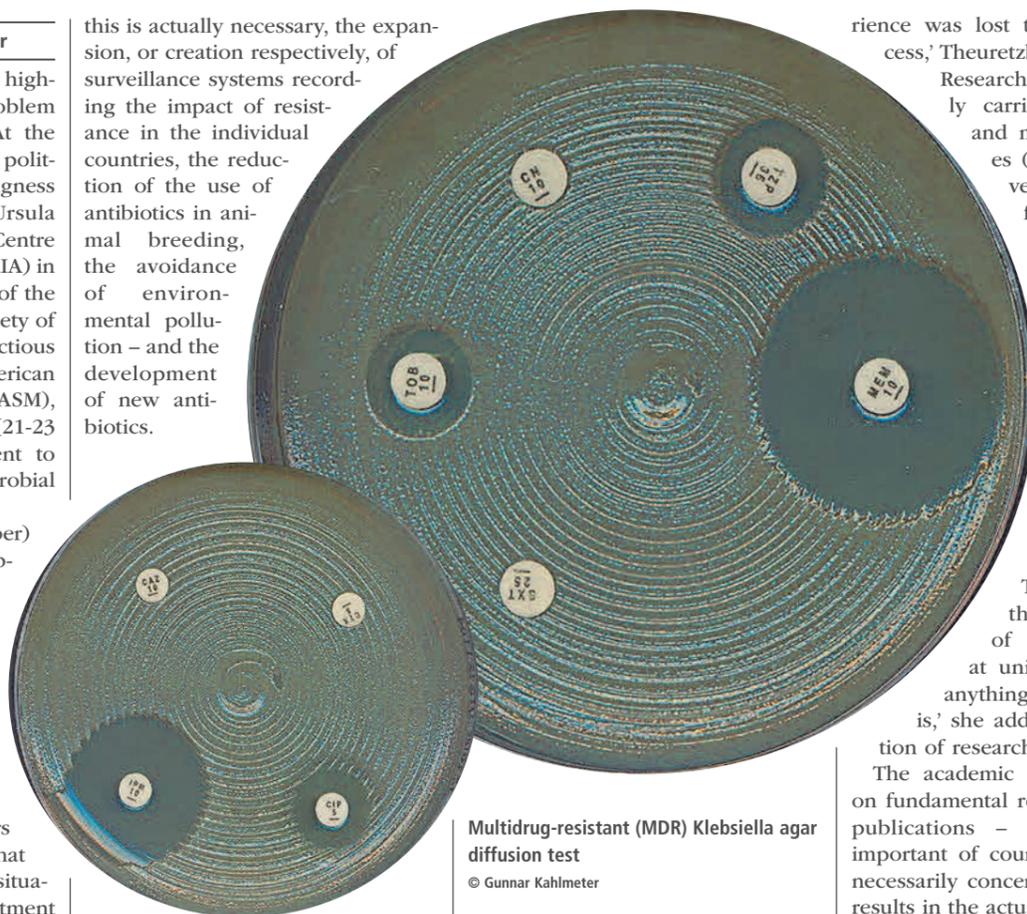
'At the moment there are mainly improvements to well-known classes of antibiotics in the pipeline,' Theuretzbacher says. 'But, there is a need to develop completely new antibiotics.' There are several reasons for this, as the Austrian microbiologist explains: Firstly, it is difficult to find new substances from a purely scientific point of view, especially against gram-negative bacteria. Their cell walls are

so complex that it is very difficult for substances to break through them – and when they do they are quickly pumped out again. Most large pharmaceutical companies have also actually withdrawn from the development of antibiotics. 'The development of new antibiotics has been without success for some time, and because it's not economically attractive, the industry abandoned this sector many years ago. A whole generation of researchers and experience was lost through this process,' Theuretzbacher points out. Research is currently mainly carried out in small and medium enterprises (SME) and at universities and state-funded research institutions. 'SMEs quickly get into trouble when they run out of money. Investors want to see quick success,' she says, explaining the disadvantages of privately funded research. The conditions for the development of new antibiotics at universities are also anything but ideal. 'There is,' she adds, 'little coordination of research.'

The academic researchers focus on fundamental research and good publications – which are also important of course – but are not necessarily concerned whether this results in the actual development of specific new drugs.'

There is a need for better coordination and for the definition of priorities.

These requests did not actually fall on deaf ears. The responsible WHO regional office is developing a strategic action plan for the European Union to contain antimicrobial resistance, and these strategic objectives also include national coordination to consolidate the required know-how.



Multidrug-resistant (MDR) Klebsiella agar diffusion test

© Gunnar Kahlmeter

so complex that it is very difficult for substances to break through them – and when they do they are quickly pumped out again. Most large pharmaceutical companies have also actually withdrawn from the development of antibiotics. 'The development of new antibiotics has been without success for some time, and because it's not economically attractive, the industry abandoned this sector many years ago. A whole generation of researchers and experience



Ursula Theuretzbacher PhD is Head of the Centre for Anti-Infective Agents (CEFAIA) in Vienna and President of the International Society for Anti-Infective Pharmacology (ISAP). The microbiologist, who studied at the University of Vienna and the University of Innsbruck, is currently work package leader in the multinational collaborative EU funded project AIDA (Re-developing old antibiotics) and in the multinational public-private partnership project DRIVE-AB (Incentivising antibacterial drug R&D, funded by the EU Innovative Medicines Initiative (IMI), and partner in the IMI project COMBACTE-MAGNET (Developing new molecules against Gram-Negative Infections). She is also founding chairperson of ESCMID (the European Society of Clinical Microbiology and Infectious Diseases) PK/PD of Anti-Infectives Study Group (EPASG), chair of a policy and scientific study group of the International Society of Chemotherapy (ISC), and member of the Executive Committee of the International Society of Infectious Diseases (ISID).



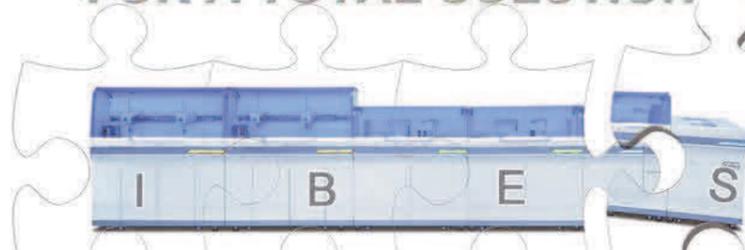
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Proposing penalties for those with lifestyle related illnesses

NHS targets obese patients

A health authority in England has sparked a major debate within the NHS after suggesting that obese patients and smokers could be refused surgery to help save money, Mark Nicholls reports

The planned restriction by the NHS Vale of York Clinical Commissioning Group (CCG) would have seen elective surgery for non-life threatening procedures – such as hip and knee operations – delayed by a year for those with a body mass index (BMI) exceeding 30.

However, the proposal is now under review after officials at NHS England – which oversees the Clinical Commissioning Groups responsible for commissioning or buying local health and care services – stepped in and ordered a re-think.

Vale of York CCG is already under 'special measures' after being labelled 'inadequate' under a new ratings system and is being offered high level support to manage and run its services.

It had initially planned to imple-

ment restrictions that would mean obese patients would receive a referral for surgery in less than a year if they lost 10% of their body weight.

And smokers would have procedures delayed for up to six months unless they gave up, or at least stopped smoking for eight weeks.

The CCG said the proposals were part of a package of measures being considered to reduce costs at a time when the local system was under 'severe pressure' and felt it was the 'best way of achieving maximum value from the limited resources available.'

NHS England has said it recognises that reducing obesity and cutting smoking benefits patients and saves the NHS millions of pounds and also that major surgery poses much higher risks for severely overweight



patients who smoke.

However, a spokesman pointed out: 'This does not and cannot mean blanket bans on particular patients such as smokers getting operations, which would be inconsistent with the National Health Service's constitution.'

NHS England has now asked the CCG to review its proposed approach 'to ensure it is proportionate, clinically reasonable, and consistent with applicable national clinical guidelines.'

In response, the CCG said it would now 'review the draft approach' and, the group added, 'hold off implementing anything until we have an agreed way forward'.

In a statement, it added: 'We will ensure any plans are implemented in line with national guidance, are in the best interests of our patients and are clinically robust.'

Chris Hopson, chief executive of NHS Providers, said that with local health services under severe finan-

cial pressure, there was a need to prioritise the treatments and procedures they pay for within the available funding but it was important to realise such decisions are not simply made on cost grounds alone.

'The decision to operate is based on a number of factors and there are often good clinical reasons why some restrictions would be placed on patients accessing treatment,' he added. 'No one will want to see patients waiting in pain longer than is clinically necessary. However, given that we are in the middle of the longest and deepest financial squeeze in the NHS' history, we are likely to see more decisions like this in future. What is important is that this is managed on an NHS-wide basis.'

The CCG estimates obesity cost the NHS in the Vale of York £46m in 2015 and comes at a time when latest figures show there are believed to be 6.8 million obese men in the United Kingdom and around 7.7 million obese women.

While the proposed restrictions – described by the Royal College of Surgeons (RCS) as 'some of the most severe the modern NHS has ever seen' – are unusual, they are not rare and serve to illustrate the financial pressures the NHS is under at present as it strives to save money.

Reports of 'rationing' of services have emerged after NHS England admitted that its provider sector overspent by £2.45 billion in 2015-



Success for implantable cardioverter defibrillator patients

Home monitoring device reduces mortality

A remote monitoring service for cardiac device patients, created by Biotronik Home Monitoring, is associated with a 38 percent reduced risk of all-cause mortality after one year across all implantable cardioverter defibrillator (ICD) indications.

In the Truecoin meta-study investigators observed these results in comparison with conventional in-office follow-up for ICD patients. Additionally, they found a 36 percent reduction in the combined risk of all-cause mortality or hospitalisation for worsening heart failure.

First presented by Dr Gerhard Hindricks, of the Leipzig Heart Centre, Germany, at the European Society of Cardiology's 2016 conference in Rome, the meta-study pooled 2,405 patients from three previous Home Monitoring trials: TRUST (Varma N, et al. *Eur Heart J.* 2014, 35 (20), ECOST (Guedon-Moreau L, et al. *Europace.* 2014, 16(8), and IN-TIME (Hindricks G, et al. *Lancet.* 2014, 384 (9943). The IN-TIME trial, showed a more than 50 percent risk reduction for all-cause mortality in heart failure patients specifically. Results of the new study extend the mortality benefit to all ICD patients.

'The results suggest Biotronik Home Monitoring is effective in helping to reduce mortality in patients with a wide variety of ICD indications, and to slow the progres-



sion of heart failure,' commented Hindricks, who is the study's lead investigator.

'We observed these benefits by analysing studies that only used Home Monitoring, rather than combining data from patients followed using systems that have differing operational features.'

'Hence, analysing individual remote monitoring systems may be preferable to global analyses.'

Hindricks further highlighted that not all remote monitoring systems are the same. The automatic, daily transmission and a specific multi-parametric data set are unique to

Home Monitoring.

'Biotronik Home Monitoring is the only remote monitoring system on the market to demonstrate a significant reduction of clinically relevant endpoints in randomised controlled trials,' the firm reports. 'Additionally, proper management guidelines (standard operating procedures) must be in place to respond to relevant patient alerts that could, for example, require changes to drug or device therapy.'

According to Hindricks, these factors appear to have a significant influence on patient well being. ■

The wave of the future: mobile learning and

A new online e-

Healthcare professionals have much to learn as medical technology continues to present them with new developments. To meet that need, medical technology manufacturer XENIOS AG, which produces sophisticated heart and lung support devices on a single platform, this year established the Xenios Campus. This aims to provide medical teams with a global digital network that 'unites all advantages of an integrating learning management system', the firm explains.

'The broad offering, encompassing tried and tested e-learning tools such as seminars, quizzes and webinars, as well as videos, documents, presentations and classroom training, creates a complete blended learning environment.'

'Since cross-border cooperation is essential, particularly in highly specialised fields, the multilingual approach of this learning programme is another clear advantage.'

Already available in several languages, it will be expanded continuously to provide internationally flexible and effective training and information.

'Comprehensive and up-to-date knowledge transfer with regard to life-saving and life-supporting devices for lung and heart is a core component of the quality and quality assurance programme of Xenios AG,' the company reports.

'In healthcare, e-learning is vital. Digital learning allows medical research results and innovations to be disseminated quickly to a wide

audience. In addition, medical staff has to be aware of regulatory issues – which differ from country to country – in order to ensure compliance.'

The e-learning industry has shown a double-digit growth annually.

'IT-supported learning in professional and continuous training is well established. Mobile learn-





Chris Hopson joined NHS Providers - the membership organisation for hospital, mental health, community and ambulance service trusts - as chief executive in September 2012 after a career in politics, commercial television and the civil service. He leads the organisation, with a particular emphasis on setting strategy, senior stakeholder management, acting as the principal public voice of the organisation and representing the provider sector on a range of NHS system level committees.

16, more than a threefold increase on the previous year.

The Vale of York restrictions echo others made in Hertfordshire, the North West and London in the past two years, where blanket referral bans were imposed on patients on the basis of their weight.

RCS president Clare Marx said: 'Smokers and overweight patients should unquestionably be helped to stop smoking or lose weight prior to surgery for their overall health.'

'We would support any attempts by Vale of York to expand its weight loss and smoking cessation programmes, but introducing blanket bans that delay patients' access to what can be life-changing surgery for up to a year is wrong.'

e-learning apps

campus

ing and e-learning apps are the wave of the future,' according to Dr Bernhard Rohleder, Managing Director of Bitkom, Germany's digital industry association, which represents around 2,300 companies.

Details: <http://www.xenios-ag.com/xenios-campus>



Zika-vaccine receives boost

A promising Zika vaccine is on its way. Themis Bioscience GmbH (Vienna, Austria), a company specialised in vaccine development, has announced that the firm will receive One million pounds sterling in funding by the innovation agency of the United Kingdom, Innovate UK, for the further development of this prophylactic vaccine and the conducting of a Phase 1 clinical trial.

The vaccine candidate uses a well-established measles vaccine vector whose core technology has been

developed at the Institut Pasteur, in France. In the past twelve months, Themis identified several suitable validated Zika antigens for the development of the vaccine.

The company's team had tested a number of candidate vaccines in animal models, and has already initiated a toxicity study and GMP manufacturing.

The main part of the programme supported by Innovate UK is the Phase 1 clinical trial, as well as the development of a thermostable for-

mulation for the vaccine.

One of the major advantages of the Themis Zika vaccine candidate is a validated as well as cost-efficient production process. The measles vector technology developed by Themis forms the basis of all current vaccine candidates advanced by the company. This allows a rapid upscaling of the very cost effective vaccine production process once the vaccine candidate has been determined. This ability is critical for a vaccine that is supposed to combat

diseases such as Zika from spreading in highly populated areas.

Additionally, the measles vaccine has already proved its high efficacy and safety on well over a billion individuals over the last 30-40 years, and the technology offers an excellent safety profile.

Under the terms of a broad license agreement with the Institut Pasteur, Themis owns the rights to use the measles vector for a wide range of indications including Chikungunya and the Zika virus.

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Aiming for anti-biofilm strategies

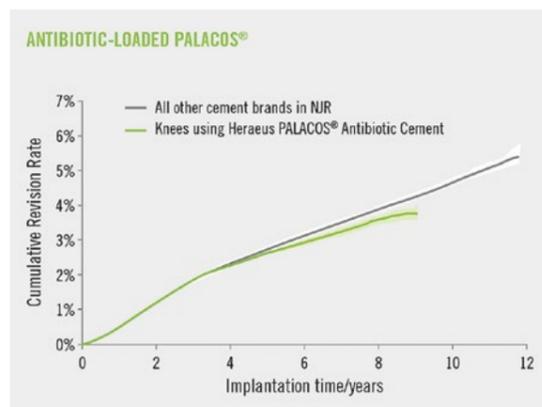
The association of biofilms with multi-drug resistance has highlighted the need for further understanding of biofilms and for anti-biofilm strategies. This September, in a satellite symposium sponsored by Heraeus Medical, manufacturer of products for orthopaedic surgery and traumatology, at the 35th Annual meeting of the European Bone and Joint Infection Society, in Oxford, the latest knowledge of biofilms and local methods of overcoming the challenge of infection was discussed.

Biofilm-related implant malfunction

In orthopaedics, bacteria may colonise a surface for months or years but remain undetected until they trigger an immune response and signs of infection. During this time, there may be low-grade infection, and symptoms such as persistent pain, stiffness, lack of range-of-movement, fibrosis, 'aseptic' implant loosening and non-union of fractures.

Biofilms and multi-drug resistance

A mature biofilm can form within 24 hours of contact with an implant and can even penetrate the surface of titanium. As the biofilm matrix is more abundant than the bacteria



Among all cement brands in the NJR Palacos R+G is superior

themselves, the biofilm must be disrupted in order to expose the bacteria to antimicrobial agents.

Multi-drug resistance may also be related to biofilm formation, for example, methicillin-resistant *Staphylococcus aureus* (MRSA) produces more biofilm than methicillin-susceptible *S. aureus* (MSSA), and therefore biofilms may magnify the cost, suffering and mortality associated with antibiotic resistance.

Superior outcome in hip and knee arthroplasty through antibiotic-loaded bone cements (ALAC)

In addition to the well-documented benefit of bone cements such as Palacos R+G in total hip replacement (THR), registry data was presented showing that significantly fewer revisions are required when that bone cement was used in total knee replacement surgery, compared to all other bone cements (Data on file. National Joint Registry (NJR, www.njrcentre.org.uk) data licensed to Heraeus Medical GmbH, Wehrheim). Palacos R+G with gentamicin also significantly outperforms plain Palacos.

Significant reduction of sur-

gical site infections (SSIs) through dual antibiotic-loaded bone cements

It is particularly important to optimise strategies for reducing periprosthetic joint infections (PJIs) in high risk patients, but which bone cement best overcomes the current challenges in PJI prevention? A quasi-randomised, double blind study was carried out, comparing the two bone cements, Palacos R+G and Copal G+C, in patients requiring haemiarthroplasty for a fractured neck of femur. There was a significant reduction in both deep and superficial SSIs with Copal G+C

compared with Palacos R+G (Tyas B, Marsh M, Molyneux C. et al. Abstract 59 presented at the Oxford meeting) explained by the previously-observed high antibiotic concentrations in wound fluid.

Extrapolating the reduction in infection rates to the entire UK hip haemiarthroplasty population would lead to healthcare savings of over £4 million.

Dual antibiotic-loaded cement does not affect antibiotic resistance profiles

A concern regarding the use of antibiotic loaded bone cements is whether they cause antibiotic resistance. The study reported no significant differences in resistance between Palacos R+G and Copal G+C. The only cases of resistance with Copal G+C were to gentamicin and clindamycin, which is as expected.

Resistance to other standard antibiotics remained low. Furthermore, Copal G+C completely eradicated infection caused by *Corynebacterium* species and *S. aureus*.

Source: Heraeus Medical manufacturer of medical products for orthopaedic surgery and traumatology. The products list includes bone cement.

Zika infections subside

'I would travel to South America any time,' virologist confirms

In Europe, the first baby with Zika-related microcephaly was born in July. The mother had contracted the Zika virus while travelling in America.

How dangerous is the virus for Europeans, particularly since many visited Brazil for the Olympic Games in Rio? European Hospital asked Professor, Head of the Immunology and Virology Research Group at Hamburg's Bernhard Nocht Institute for Tropical Medicine.

Asked, in terms of the Zika virus, whether one should be cautious about visiting South America, Prof. Schmidt-Chanasit responded with little doubt: 'I would definitely go. The Zika virus has in no way affected the security of travellers – except pregnant women. There are many diseases that are much more problematic than Zika fever, such as dengue or malaria. The only group I would recommend abstaining from a visit to those countries are women during the first three months of pregnancy since there is a low risk of harming the foetus. This fact has caused a lot of concern and received considerable media attention. Generally speaking, however, a Zika virus infection is not a problem for non-pregnant persons. And most people do not get ill. Therefore I would travel to South America anytime.'

Might the disease be sexually transmitted?

'The main transmission vector is the mosquito. Sexual transmission may

happen but it is very rare – a marginal phenomenon. Of all Zika virus infections known in Germany one documented infection was transmitted sexually. If it does happen it's always transmitted from the male to the female. There is no known case the other way around. Men who are known to carry the virus should always have safe sex with pregnant women. The virus can be detected in sperm for at least three months, maybe even a bit longer – we need further research on this issue. Thus men who were tested positive and have unsafe sex with pregnant women are the only group who pose a problem.'

Could this mean that a virus transmitted to a woman will not cause damage in any of her subsequent pregnancies?

'There is no indication that the virus will persist in women and cause problems or malformations in later pregnancies.'

How can we protect ourselves from the mosquito?

Sprays, mosquito nets, long-sleeved shirts and air-conditioned environments offer the best protection. The spray should contain diethyltoluamide (DEET) because of its long-lasting effectiveness and because you can spray it on your clothes. Beyond these, there are anti-Zika programmes that need to be organised by public health authorities.

Are people carrying the Zika virus more at risk of developing Guillain-Barré syndrome?

'No. Today the virus has spread basically all over the world. In many countries it has been endemic for a number of years; in South East Asia it has been known in Thailand for decades. The hysteria fired by the media is incomprehensible. Currently, Europe and Australia are the only non-affected continents, but we do expect imported and locally acquired infections during the summer. But there will not be an outbreak comparable to the one we've seen in Brazil. Therefore, there is no reason to worry in Europe.'

'This disease also occurs with other infections, such as *Campylobacter jejuni*. It does not occur more frequently after a Zika virus infection than after any other infection – as was recently shown with regard to the outbreak in French Polynesia. This auto-immune disease is not new to us.'

What about European Zika infections?

'Since May 1 the infection has to be reported under the German Infection Protection Act, for example. In this country about 100 Zika infections were reported.'

Is there a risk of a pandemic?

'No. Today the virus has spread basically all over the world. In many countries it has been endemic for a number of years; in South East Asia it has been known in Thailand for decades. The hysteria fired by the media is incomprehensible. Currently, Europe and Australia are the only non-affected continents, but we do expect imported and locally acquired infections during the summer. But there will not be an outbreak comparable to the one we've seen in Brazil. Therefore, there is no reason to worry in Europe.'

Then why was an international health emergency declared?

In February it was still not clear whether there was a connection between microcephaly and the Zika virus. Therefore it was correct to declare the emergency. It triggered an intensification of research efforts and the connection was soon estab-



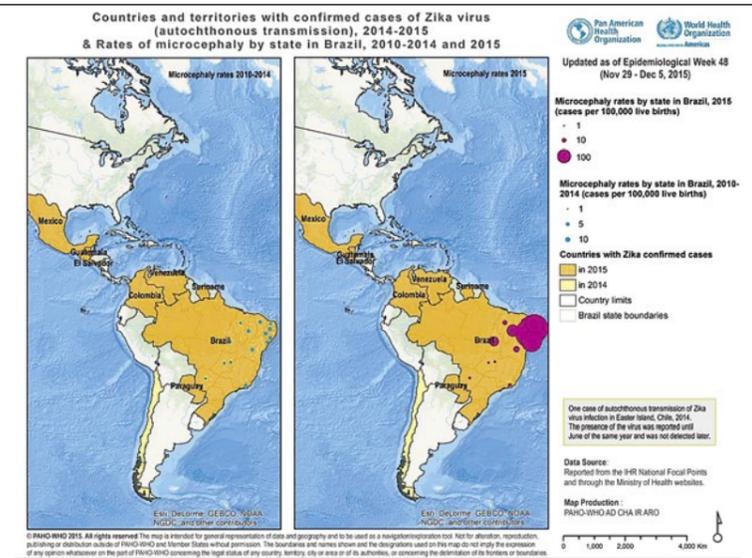
Jonas Schmidt-Chanasit MD gained his doctorate at the Charité Berlin Medical School. Still a student, he spent time as a researcher at Kasetsart University in Bangkok. In 2006/2007 he was Research Fellow at the Institute for Medical Virology in Frankfurt am Main, Germany, and then became Head of Virology Central Diagnostics at Bernhard Nocht Institute Hamburg. In 2010 qualified for university professorship in virology at Johann Wolfgang Goethe-University, in Frankfurt am Main, and was appointed professor in arbovirology* at University of Hamburg in 2015.

* Relating to any of numerous viruses that replicate in blood-feeding arthropods, such as mosquitoes and ticks

lished. Declaring the emergency was the right step. But obviously it is very different from Ebola, which killed 70 percent of the infected persons.'

When will there be a safe vaccine?

'Unlike with Ebola there was no immediate vaccine candidate for Zika. However, now there is one that's currently being tested on monkeys. Clinical studies, about to start shortly, will take a few years to complete. Thus any vaccine won't help in the current situation. However, the epidemic is subsiding in Colombia and Brazil. The vaccine research is an investment in the future, if there is another outbreak in 20 or 30 years. Most people in South America are immune, the so-called herd immunity, thus there is no, or only a low, intensity virus circulation. Consequently the vaccine is not that crucial because it's too late for the current epidemic.'



Frontline medical advances

Virology is now a key discipline

Virology is fast emerging as a key discipline within modern health-care against a backdrop of a shifting global demographic and the impact of climate change, Mark Nicholls reports

The study, diagnosis and treatment viral infections has grown in importance at a time when a panel of scientists and public health experts, convened by the World Health Organisation, listed seven viruses in the top 10 emerging pathogens likely to cause severe outbreaks.

European hospitals and health professionals also face ever-more challenging viral infections as the world population becomes more mobile. Along with HIV, Ebola and Zika – often in the headlines – hantavirus and hepatitis E virus infections are more prevalent and being seen more by European health services.

With medical virology at the forefront of diagnostic advances, UK clinical virologist Dr Mark Zuckerman explained that the perception is that some of these viruses are new, yet in reality have been around for many years but have only more recently gained a higher profile.

Following its outbreak in Brazil, with its huge population, Zika's impact, for example, has magnified with its presence now seen in the Americas and reported in Europe. Earlier, however, it had emerged in smaller populations in the South Pacific islands.

Zuckerman, who heads Virology at King's College Hospital, London, said some of the 'time-honoured' viruses are now turning up in unusual situations, but more significantly some of the rarer viruses are now appearing in unexpected locations.

Greater global mobility and travel, as well as climate change, are factors within this, he added.

As the challenge of tackling viruses grows, health systems need to adapt to meet those challenges, he pointed out, becoming proactive as well as reactive and embracing new techniques and advances in molecular diagnostic testing and point-of-care testing.

'Medical virology continues to be at the forefront of technological advances. With the on-going development of new laboratory techniques, antiviral drugs, vaccines and emerging pathogens, the speciality is always evolving, making it both intellectually challenging and exciting.'

In healthcare terms, clinical virology is a relatively new specialty drawing together clinical work, laboratory liaison, research, development and teaching.

Clinical virologists concentrate on the diagnosis and management of patients with viral infections, with rapid diagnosis using molecular based tests, monitoring resistance to antiviral drugs and research and development key parts of the speciality.

'Patients are generally in hospital or the community with acute or chronic viral infections,' Zuckerman said. 'They may have travelled to areas where specific virus infections are endemic; may need screening for viral infections that cause complications in pregnancy and after organ transplantation; and may be immune-compromised and need monitoring as they are at risk of complications of a variety of viral infections, some of which are latent and may reactivate.'

As well as the diagnosis and management of acute infections, there

avian flu and pandemic influenza.

Clinical virologists also work closely with laboratory scientists in day-to-day diagnostics involving serological assays and molecular tests, including polymerase chain reaction (PCR) and sequencing and also ensure antiviral drugs are prescribed and used appropriately.

'Virologists have a role in infection control of norovirus, viral gastroen-

teritis and flu virus infections, working with microbiology colleagues and infection control nursing teams.

'The multidisciplinary nature of the job involves daily contact with a variety of healthcare professionals including hospital doctors, general practitioners, microbiologists, trainees, infection control nurses, healthcare and clinical scientists and public health doctors,' said Zuckerman,

who also chairs the Clinical Virology Network (CVN), a co-ordinated group of laboratories in major centres in the UK and Ireland, which promotes the interests of clinical virology, providing evidence-based and practical virology advice on viral infections and helps to establish and maintain the standards of practice amongst its membership and promotes a uniform approach to surveillance. ■



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The IVDR will bring about extremely significant changes

IVDs under the microscope

New EU legislation gives manufacturers five years to meet strict standards. That may not be enough time, John Brosky reports



European regulators have turned the world of *in vitro diagnostics* (IVDs) upside down with new legislation that will come into effect at the end of this year.

The stricter rules are especially tougher for advanced molecular diagnostics and lab-on-chip assays used in the clinic to help identify a patient's pathology. But also coming under scrutiny for the first time will be DIY pregnancy kits or at-home nutrigenetic tests that have not been covered by the current regulations.

Outraged by the scandal over breast implants that fraudulently used industrial-grade silicon and with on-going concerns for metal-on-metal hip implants, the European Parliament launched a total overhaul of the directives for awarding the CE Mark for medical devices and

in vitro diagnostics (IVDS) devices.

The reform movement in Brussels has resulted in nothing less than an upheaval of the landscape for manufacturers.

For example, all IVDs will need to be recertified, including products already on the market. And where the current EU directives allowed a self-certification of the vast majority of tests, the new IVDR now requires 80 percent of all assays and reagents to undergo a strict level of independent scrutiny that runs up the supply chain to include subcontractors and software associated with the product.

While there is a five-year transition period provided in the new laws, that may not be enough for many manufacturers, according to Gert Bos, the Executive Director

at Qserve Group, a medical device consulting firm based in Amsterdam. He also is the past-President of the European Association of Notified Bodies for Medical Devices.

The notified bodies are the gatekeepers for access to the EU market, independent companies accredited by a Member State to assess whether a product to be placed on the market meets the preordained standards.

'Most manufacturers will have to revisit all technical files and the quality systems for all their devices, they will need to generate additional clinical and performance evidence,' Bos wrote in a detailed guide entitled, *Dos and Don'ts: How to prepare for and implement the upcoming In Vitro Diagnostic Regulations (IVDR)*.

The white paper was co-authored by Erik Vollebregt, a partner at Axon Lawyers in Amsterdam, an expert on EU regulation and the author of the widely followed blog, Medical Device Legal.

With permission of the authors, this article extracts highlights from the white paper.

'The IVDR will bring about extremely significant changes. Most critical is the full revision of the classification system into a rule-based risk classification matrix. In contrast to the current situation, this means the vast majority of products will need to be evaluated by the notified bodies.'

As the result of greater scrutiny since 2013, the number of notified bodies has been dramatically reduced, a critical issue for manufacturers. Bos estimates that, by the end of 2016, there will be from 40 to 45 certified notified bodies remaining from approximately 80 before the 2011 breast implant scandals that provoked the reform movement for EU regulations.

'Manufacturers must be aware that they may need to change a notified body as a result of this development, and act accordingly if their current notified body is not able to support the manufacturer anymore,' he cautions.

In addition, he said that the

administrative burden will increase substantially for manufacturers as a result of registration requirements and the implementation of a Unique Device Identification (UDI) system. 'Consequently,' he wrote, 'manufacturers must take a proactive approach to the new regulation, plan and budget for the transition of existing devices in a timely and detailed way, and allocate resources for this effort.'

IVDR shares many new features with the upcoming EU Medical Devices Regulation (MDR) proposal, such as new supply chain requirements and the implementation of a central database (EUDAMED)

Here are the four major developments specific to the IVDR field highlighted by Bos and Vollebregt.

1. Extension of the concept of *in vitro* diagnostic devices to include tests of 'indirect medical purpose' and 'prediction' to include nutrigenetic tests and lifestyle tests, which are not covered by the current IVD Directive.

2. IVDs will no longer be subject to the list-based system currently in the IVD Directive, but to the risk classes developed by the Global Harmonisation Task Force (GHTF), dividing the landscape of IVDs into risk classes from A (low-risk) to D (high public and high patient risk) with seven classification rules.

With notified bodies having to perform conformity assessment on all but class A devices, the landscape is dramatically changing in terms of files to be reviewed and audits to be performed pre- and post-market.

3. The conformity assessment routes for IVDs are amended to fit the new classification logic. IVDs that do not fit any of the other classification rules fall into class B and have to be certified by a notified body. This is a major change compared to the IVD Directive, which



Gert Bos is an influential voice for European regulatory issues. For many years he served as the President of the Notified Body association TEAM- NB, and as Vice Chair of the Medical Notified Body Forum. Until 2016 he was the Head of Regulatory and Clinical Affairs of British Standards Institute for Medtech. Currently he is the Executive Director and Partner at Qserve consultancy.

allows such IVDs to be self-certified. As a consequence 80 percent of all IVDs will need to be certified by a notified body under the IVDR, as compared to 20 percent currently under the IVD Directive.

4. Clinical performance studies will be required to support the CE mark under the IVDR. As a consequence IVD manufacturers will need to produce significantly more clinical evidence. The IVDR will contain rules for interventional clinical performance studies and other clinical performance studies that largely overlap with the clinical studies regime in the MDR proposal.

It is crucial for manufacturers of IVDs currently on the market to plan the generation of additional clinical evidence well, and timely assess what clinical evidence will likely be required, how long it will take to generate this and plan ahead for notified body slots for conformity assessment.

In short, the clinical performance evaluation will include not only the classic clinical performance and analytical performance, but also scientific validity. With this change, the first steps towards manufacturers becoming fully responsible for the clinical utility of their devices are initiated. ■

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The level of mutated DNA in blood corresponds to

Liquid biopsy detects tumour changes in

New findings from a scientific collaboration between the German Cancer Research Centre (DKFZ), the National Centre for Tumour Diseases (NCT) Heidelberg and the Thoraxklinik Heidelberg suggest liquid biopsy as a promising tool to monitor lung cancer patient tumours early. Scientists associated liquid biopsy readouts with clinical data and could track tumour responses to cancer drugs in real-time.

Although currently considered the 'gold standard', tissue biopsies are not without limitations. Thus, in recent years, a new alternative, liquid biopsy, has gained attention. When cells die, they release their DNA (so-called cell free DNA, cfDNA) into the bloodstream. For tumour cells that die after therapy, the cfDNA contains mutations that could be detected and analysed with PCR or sequencing tools for non-invasive diagnosis.

However, the sensitivity and clinical information provided by liquid biopsy is less clear, prompting the group to investigate further. By collaborating with partners at the Heidelberg Thoraxklinik, the DKFZ

researchers recruited a focused cohort of 16 lung cancer patients, all carrying prominent mutations, and were undergoing tyrosine kinase inhibitor (TKI) treatment. Over a period of up to two years, the researchers collected sequential blood plasma samples from each patient and extracted the DNA.

By analysing the data, the scientists made three interesting observations. First, the number of mutated alleles in patients changed according to the clinical course of the disease. For example, in one patient, the initiation of TKI therapy was paralleled by a drastic and immediate (within 26 hours) rise of mutated cfDNA in the blood plasma, prob-

New system for low volumes of ultra-pure water

The compact mini lab water system

With a unit width of just 11 inches, the new, compact arium mini water system, from lab and pharma equipment supplier Sartorius delivers a flow rate of 1 liter per minute and has been designed for ultrapure water requirements of less than 10 liter per day.

Feed water is supplied via a 5-liter bag, integrated on the side of the system, which, is optimal for storing purified water, the company reports. Sartorius continues: 'The closed bag-tank system prevents secondary contamination while ensuring consistent long-term water quality. Uncomplicated exchange of the bag also facilitates upkeep of the system and considerably reduces maintenance time compared with conventional tank systems. The bag-tank does not require any hazardous cleaning chemicals, further increasing user safety as a result.'

The system also has a high-resolution, touch-activated colour display. Simple icons guide users intuitively through the menu. A favourites function automatically stores the volume last dispensed, thus increasing efficiency and preventing errors during repeated dispensing of identical volumes.

Users can choose between two models to suit individual requirements. The standard arium mini is independent of a permanently installed water tap, receiving water via the integrated bag, filled by a built-in pump.

During this process, pre-treated water is pumped into the bag automatically and is thus used as feed water for the production of ultrapure water.

With expanded features, the arium mini Plus is directly connected to a feed water tap, with water first treated by a pre-treatment cartridge

combining activated carbon and a reverse osmosis module, then is safely stored in the system's integrated bag. Finally, ultrapure water is produced via an arium Scientific purification cartridge. ■

For analytical and especially critical applications, such as HPLC, arium mini can be optionally ordered with an integrated UV lamp (185/254 nm) to ensure water is virtually free of organic components. Photo: Sartorius AG, Göttingen



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to patient outcome

ects n real time

ably indicative of an effective therapy response that resulted in many cancer cell deaths. Interestingly, this 'peak' declined shortly afterwards, suggesting that TKI therapy had its greatest impact only during the first few days of treatment.

Secondly, the researchers found that low, or absent levels of mutated cfDNA associated with sustained periods where the disease remained under control and the tumour did not grow. Finally, in patients whose tumour relapsed and who died soon afterwards, the mutated cfDNA levels were found to be increasing rapidly over short timeframes.

These findings highlight liquid biopsy's sensitivity in detecting and reflecting tumour changes in real time, while providing the advantages of being less invasive. The molecular data provided by this method might also help inform physicians to make earlier decisions on therapeutic strategies. ■

A one-step system for faster turnaround of hospital samples

A new molecular diagnostics system is revolutionising analysis of hospital samples across an area of northern Italy.

The Greater Romagna Area Hub Laboratory has recently installed the Beckman Coulter DxN VERIS Molecular Diagnostics System and is already reporting improved workflow and quicker turnaround time for results.

Laboratory director Professor Vittorio Sambri explained that the system is being used for the four key tests of HIV-1, HBV (hepatitis B virus), HCV (hepatitis C virus) and CMV (cytomegalovirus) in his centre, which delivers all microbiology testing, bacteriology, serology investigation and molecular diagnostics for virology for 11 hospitals with 4200-plus beds between them, serving the 1.2m population of the Greater Romagna region.

The lab, which opened in 2009, upgraded to the Beckman Coulter DxN VERIS Molecular Diagnostics system earlier this summer.

Professor Sambri explained: We decided to go for the Beckman Coulter system for the analytical and organisational features it offered, as well as price. However, cost was a secondary issue. The greatest benefit has been the organisation of the workflow which is much easier, it is more linear and on-demand so you do not need to batch samples, which means we can provide reports to cli-

nicians in a faster and more timely way.”

With a simplified, flexible workflow and single sample random access, the DxN VERIS Molecular Diagnostics System is an automated system for routine core lab work that combines all the sample DNA extraction, purification, assays set up and analysis in a four-step workflow: load samples onto rack; place on the DxN VERIS System; hit run; read results 70 minutes later (DNA

or 110 minutes later (RNA).

By reducing manual intervention, and automating the steps from sample loading to reporting of results, the DxN VERIS system has the potential to revolutionise laboratory workflows and reduce time to results.

There is no lengthy set-up with all consumables/reagents refrigerated on-board, enabling better use of staff resources, and random access is one-step sample loading per specimen as compared to the current batch systems.

The DxN VERIS system enables each sample to be independently tested, with results reported immediately when the individual test is complete, eliminating the wait time associated with batch results reporting.

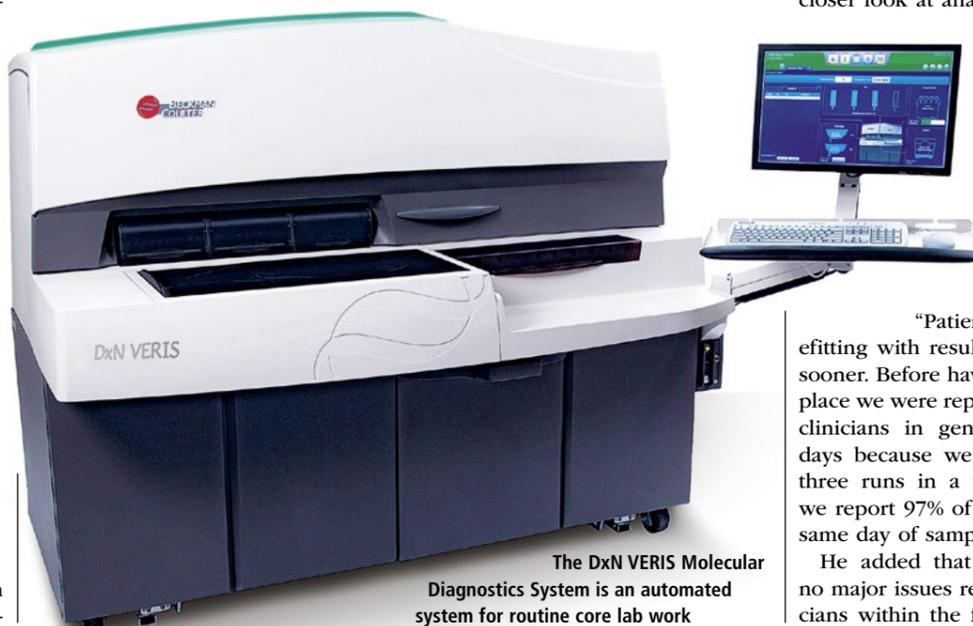
“From an organisational point of view, it is much faster and easier,” added Professor Sambri.

With the installation still relatively new, the Italian team is working closely with Beckman personnel on calibrations and controls and Professor Sambri has asked for a closer look at analysis of HBV samples, for example.

“With HIV and HCV the system is really robust and with CMV the number of indeterminate results is extremely low,” he said.

“Patients are also benefiting with results provided much sooner. Before having this system in place we were reporting results with clinicians in general within three days because we were performing three runs in a week. Right now, we report 97% of results within the same day of sampling.”

He added that there have been no major issues reported from clinicians within the first months of its



The DxN VERIS Molecular Diagnostics System is an automated system for routine core lab work



Professor Vittorio Sambri is Associate Professor of Microbiology, DIMES, University of Bologna and Head of the Unit of Microbiology at the Greater Romagna Area Hub Laboratory. He is involved in research related to outbreaks of Chikungunya fever and West Nile virus in Emilia Romagna Region in the recent years, and of new and emerging vector born infectious diseases in Italy. Professor Sambri is Vice President of the Association for the Study of the Infections and his work has resulted in more than 180 scientific publications in international peer-reviewed journals.

use but the laboratory staff will be meeting with clinicians in the near future to fully evaluate the Beckman system.

Jaime M. Menendez-Humara, global strategic marketing director for Molecular Diagnostics, Beckman Coulter, said: “The DxN VERIS system ensures the ability that laboratories can run any of the four available assays, any sample, at any given time.

It's the ultimate in ease of use, giving the laboratory manager or director the choice of how to best optimize their team to do the work they want, when they want.”

The quiet force to optimise existing resources

OPINION: The value of point-of-care

Some significant changes in the European hospital sector have occurred over the last 20 years. The necessity to contain the exploding costs in particular has led to a reduction in the number of hospitals and hospital beds, and staffing levels have also been affected by the many cost cutting measures. This has not been without its consequences, as we now know, writes Ludwig F Rutten.

“Whilst objects such as beds, medical devices or other materials may be easy to acquire, lease or hire, the situation is different when it comes to human resources. There is a lack of nurses, doctors, medical engineers and IT specialists, across the entire European employment market. Nothing damages a hospital's reputation more than a rating that states it does not provide adequate patient care. There has been no getting away from it: Long waiting times and deteriorating care caused by a lack of staff on the wards are standard in many hospitals. This is particularly frustrating for all concerned when the respective budget is actually in place but suitable staff cannot be found.

There are obviously various ways to solve these problems. The easiest, but not necessarily most effective solution is to put the blame and responsibility on the ‘system’ and to wait until the system solves the

problem. Actually, this tends to be the most common approach!

A much more successful line is to utilise improve productivity in existing resources more efficiently. A closer look at workflows repeatedly reveals a multitude of activities that originated in the past, but the necessity of which has never since been questioned.

One of the factors that could

lead to a significant improvement in the situation is the handling of laboratory tests beyond the laboratory. A look at the entire process for some essential laboratory tests shows, without a doubt, that some tests could benefit from substantial improvements if the analysis was carried out on site, i.e. via a point-of-care test (POCT), rather than by a centralised service provider – the laboratory.

Some excellent examples of POCT can be found in the A&E department. Nowadays, to determine a troponin level via a POCT, within 15 minutes, is no longer a problem. However, the majority of A&E departments still send samples to the central laboratory. This results in long waiting times, unnecessary additional work for nurses and doctors and in patients spending far too

much time in treatment rooms. What applied in the past is still relevant today: time is money. A solid analysis of the current situation and the willingness of all those involved to allow changes can lead to considerable increases in efficiency.

Naturally, it would be wrong to say that POC does not exist in European hospitals at all; it is already in practice in many places. The most important examples are blood glucose measuring systems and blood gas analysis. The question is, whether the right systems are being used. Finding systems that actually worsen a situation, instead of improving it, is not uncommon. Systems must fit into the workflow. In other words: When the decision is taken to establish POC, the optimum work process must be defined before the required systems are chosen.

Whether or not a POC concept supports workflows in a meaningful way depends to a large part on the performance of the IT systems used. Modern systems specifically developed for POC offer the user many opportunities to make working with the systems as easy and safe as possible. However, for this, an IT system that supports the different opportunities offered by POCT systems is a prerequisite. The latest systems make the use of pen and paper completely redundant. It makes no sense to make laboratory test results available more quickly if old, standard forms are then used to document patients' results,



Equipment advances according to needs. POCTs can increasingly be carried out beyond a centralised service provider, easing pressures on hospital or external laboratories



Currently co-owner of POCTmedconsult GmbH, in Germany, Ludwig Rutten has more than 10 years' experience in marketing Point of Care (POC) products. In a previous role, for example, he initiated several studies and workshops on process optimisation and POC.

or for the obligatory quality control documentation still required in some countries. A combination of ‘modern’ with ‘stone age’ would be counterproductive in this case.

What we would like to tell the observant reader with this contribution is that the integration of POC can only be successful if thorough preparation takes place beforehand. The change to POC is more than a discussion as to whether a system is technologically suitable to carry out certain types of analyses or not.

As the resulting profitability of a POC project directly depends on the increase in efficiency expected, all those involved should take enough time for a detailed analysis of the current situation and the results to be expected. If everything has been done properly POC will be the quiet force that helps to utilise the existing resources in the best possible way for a long time to come. ■

Computerised blood bank transfusion management and administration

An integrated single database solution

According to a 2007 World Health Organization report*, patient misidentification was cited in more than 100 individual root cause analyses (January 2000 to March 2003) by the USA's Department of Veterans Affairs National Centre for Patient Safety. Major areas where patient misidentification can occur include drug administration, phlebotomy, blood transfusion, and surgical procedures.

In today's fast-paced, highly regulated transfusion service, safe products must meet the diverse needs of a complex multisite facility as well as highly specialised needs of a single facility.

'SCC Soft Computer's Blood Bank Transfusion Service Information Management System, provides critical safety functions throughout the system, allowing users to focus on what's important: providing safe blood components, tissue, and derivative products to their patients,' the supplier of SoftBank reports.

The systems range of features streamline many routine, manual, and time-consuming tasks associated with blood bank and blood donor protocols, the firm adds. 'These timesaving improvements translate into revenue for transfusion services departments of all sizes.'

The system also provides a comprehensive, cost-effective centralised pre-transfusion testing and inventory management software solution. The database management system is also reported to provide fast, direct linking between records and transactions, dramatically increasing levels of security and integrity when per-

forming and documenting activities and events.

SoftBank has FDA 510(k) clearance as a Class II Medical Device and provides a controlled and documented process for blood bank testing and issue of products.

'With the versatility of SCC's SoftID.Tx [also FDA 510(k) cleared], users can add positive patient identification (PPID) into their existing workflows. By leveraging the power of the integrated platform, blood banks and transfusion services can streamline their processes. The parameter-driven setup allows the builder to create a workflow perfectly suited to the users' routines, or to create a totally new workflow... The design is up to the individual client.'

Unlike stand-alone transfusion administration systems—or HIS/EMR vendor-provided transfusion administration systems, this is a fully integrated module of SCC's SoftBank blood bank and transfusion service information management system, thus yielding important patient safety and workflow advantages for clients who elect to implement a PPID solution for transfusion administration.

Support bedside transfusion



SoftBank streamlines many of the routine, manual, and time-consuming tasks associated with blood bank protocols. These timesaving improvements translate into revenue for your transfusion services.

administration and bedside collection of patient vitals during the blood transfusion process, eliminate manual entry, and automate workflow with the fully integrated SoftBank/SoftID.Tx solution.



According to Gilbert Hakim, SCC Soft Computer CEO, SoftBank, a centralised transfusion service management system, was designed and developed in 1992. 'Over the years, SoftBank has evolved to keep pace with regulatory changes and with the addition of interfaced instrumen-

tation. Two reasons for the product's success are SCC's commitment and funding for steady and constant improvement of SoftBank for more than 20 years, and input from our dynamic client base.'

* <http://www.who.int/patientsafety/solutions/patientsafety/PS-Solution2.pdf>

Point of care testing for critically ill adults

CPOCTs in development

Report: Lisa Chamoff

Waiting for test results can be a minor inconvenience for some patients, but for those who are critically ill, timing matters.

At the recent CPOCT International Symposium in Copenhagen (21-24 September) Dr Craig Lilly, a professor of medicine at the University of Massachusetts spoke about the point-of-care testing market, outlining currently available testing for critically ill adults, and also under development.

'Knowing the test value will be impactful for patients' experience and outcomes,' Lilly said. 'Sometimes it doesn't matter if you know now or know within a few hours. There is some testing where knowing right now matters.'

Lilly discussed tests currently used in the USA, such as blood glucose testing, and the frequency of use, as well as tests that might be available in the future. He also spoke of the value proposition of future testing — specifically, which tests will make sense to develop further despite the high costs of development.

Some tests currently in development make sense for investment, the professor pointed out. Tests in development are centred on infectious diseases, and there are also tests routinely used for acute coronary symptoms, or for neurological emergencies, that are not currently available in the point-of-care format, but which are likely to be widely used in the future.

'We currently don't have tests for neurological emergencies and we really need them,' Lilly said.

Many facilities are not equipped

with easy ways to test for problems that require urgent action, and that's where the value lies in developing point-of-care tests, he added. 'If you are in nursing home and develop

chest pain in middle of night, the nursing home can't do an electrocardiogram and blood work. They put you in an ambulance. That is both inconvenient and expensive.

If you can do tests at the point of care, within the skilled nursing facility, the avoided costs more than justify making the point of care test available.'



Craig M Lilly MD is Professor of Medicine at the University of Massachusetts Medical School in Worcester, Maryland



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Sonic boom with bubbles

Illuminating blood vessels, opening the blood-brain barrier and delivering drugs. What will be the next big thing that tiny microbubbles can do? John Brosky investigates

In the beginning there was the bubble, even if no one was quite sure what they were supposed to do with it. Once injected into the blood stream, it was clear to anyone conducting an ultrasound examination that these microbubbles introduced by Bracco Imaging under the name SonoVue (sulphur hexafluoride microbubbles) absolutely and instantly highlighted blood vessels.

Twenty years later, microbubbles are popping up everywhere as clinicians continually demonstrate new and innovative applications, not only for detecting and diagnosing disease, but more recently for treating it as well. Tiny microbubbles in the blood have already revolutionised medical imaging, yet hold a promise for going much further.

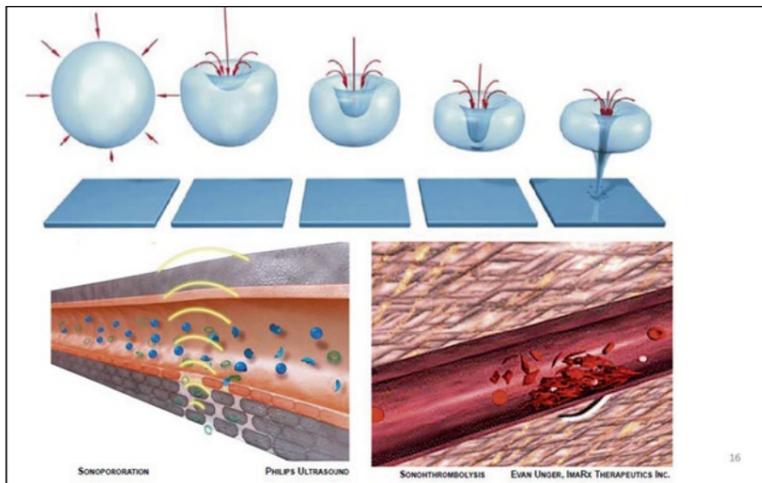
In September 2016 Bracco brought together in Geneva scientists and clinicians from globally renowned research centres for the 9th Global

R&D symposium entitled Bubble World to explore the numerous opportunities for microbubbles, not only to see-and-treat disease in the human body, but to explore and discuss future potentials for medical and non-medical applications.

Diagnostic Imaging

There is a long list of things where microbubbles have proven to add value to clinical practice, according to Professor Peter Burns, Chairman of Medical Biophysics at the University of Toronto.

One of the first, the most successful, and most widely used application of microbubbles is for the identification and differentiation of cancer from other vascular entities. Cancerous tumours are known to create their own blood vessels, but no one had ever seen so quickly and clearly these micro networks until microbubbles illuminated them



Bubbles now work in various explorations

on the ultrasound screen. SonoVue highlights where there is blood flow and where blood is not flowing but should be, Burns explained. Ischemia imaging with ultrasound in combination with bubbles can answer clinical questions such as whether myocardial function has been successfully restored after an intervention.

A closely related area is imaging inflammation to identify malignancy, he said, as an emerging practice and an alternative to the current standard of care. Following conventional practice, he said, 'Younger people being diagnosed with this condition will receive 20 abdominal CT exams by the time they are 20 years old.'

'Bubbles are the only true intravascular contrast agent in diagnostic medicine and magnificent amplifiers of ultrasound with a sensitivity that is capable of identifying individual bubbles,' Burns said in his presentation.

Therapeutic applications of micro bubbles

In November 2015 Professor Kullervo Hynynen was part of a scientific team that achieved a world-first in human medicine by using microbubbles to open temporarily the blood-brain barrier. The technique opens a new approach for delivering drugs to fight brain cancer, as well as creating a novel approach to treating neurological disorders, such as Alzheimer's disease.

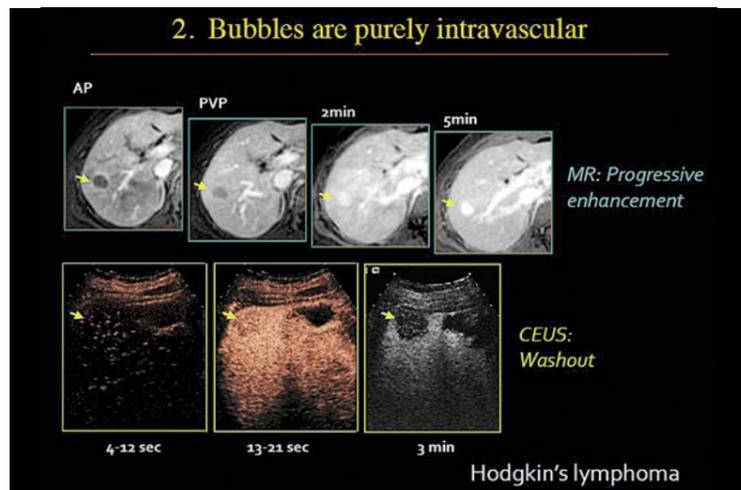
The Chair of the Image-Guided Therapy group at the University of Toronto, Hynynen worked with colleagues at the Sunnybrook Health Sciences Centre to apply focused ultrasound beams at a point where microbubbles were circulating. The vibration of millions of bubbles under the sonic signal caused the tight network of interlocking cells to loosen enough for a limited flow to pass out of the blood vessel and into brain tissue. Today, only 2% of drugs for treating a brain tumour actually reach the tumour because they are blocked by the blood-brain barrier.

Opening this barrier with microbubbles allows a significantly greater dose of chemotherapy to penetrate to tumour tissue. 'This also presents the possibility to deliver novel drugs, such as DNA-loaded nanoparticles, viral vectors, or antibodies to the brain to treat a range of neurological conditions,' he told colleagues in Geneva.

Piercing this barrier also allows the body's own natural defence mechanisms to fight disease. Hynynen said researchers found, in animal studies, a partial restoration of memory after brief blood-brain barrier opening, which they believe is the result of two effects. First, the body's own agents of the immune system were able to attack and reduce the amyloid plaque that is characteristic of Alzheimer's disease, and second, the treatment stimulated growth of neurons.

Jessica Foley, the Chief Scientific Officer at the Focused Ultrasound Foundation in Charlottesville, Virginia told scientists at the symposium that the high-intensity focused ultrasound (HIFU) platform for one company has already received regulatory approval to treat the brain and that many other companies are now seeking approval. 'There are more than 35 companies advancing HIFU technology, an exponential growth after many years of this being a research tool,' she said, adding that 100,000 patients have been safely treated using HIFU to destroy tumours.

'Breaching the blood-brain barrier opens up a new frontier to non-invasively deliver therapies for a number of brain disorders,' she said. 'Microbubbles loaded with a therapeutic and activated with focused ultrasound have the potential to

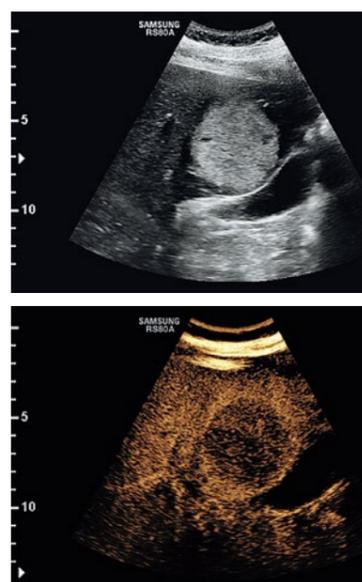


Ultrasound: The requirements for high-end equipment

Only convincing with contrast

Contrast enhanced ultrasound is part of clinical routine and makes a substantial contribution towards increasing the significance of tissue and organ diagnosis with ultrasound for difficult cases. 'CEUS allows us to optimise our daily routines, to achieve the correct diagnosis faster and to improve solutions for unclear cases,' explains Professor Dirk-André Clevert MD, head of the Interdisciplinary Ultrasound Centre at the Ludwig Maximilian University of Munich. The emergence of new competitors in the market and increasing competition between providers further enhances technological innovations.

Ultrasound, and specifically contrast ultrasound, is not inferior to cross-sectional imaging. Particularly in cases where the result of a CT or MRI scan is not clear, ultrasound often provides an important second opinion. Unlike a primary radiological diagnosis contrast ultrasound does not just deliver a snapshot but an entire image or, as Clevert puts it, the entire news programme, from the welcome to the weather forecast. 'The advantage of ultrasound is its high temporal resolution, which really allows us to observe how the microbubbles flow over a period of several minutes. We can see the process and also observe what hap-



Liver lesion of a neuroendocrine tumour in the B-image and with CEUS in arterial and later phase

pens afterwards, which is especially helpful in cases where the process is not quite typical.'

In his opinion, the comparison between cross-sectional imaging and ultrasound is also impaired because CT or MRI scanning with contrast media is often compared to native ultrasound. Comparing both technologies without contrast media would be much closer to the truth and reality.

For Clevert it is therefore logi-

cal that CEUS is now licensed in its primary field of application for liver diagnostics, and specifically to detect and characterise liver lesions, in the USA, Canada and Brazil, with Mexico soon to follow this example.

Clevert has also experienced the benefits of off-label use of CEUS, especially for children. The use of contrast-enhanced ultrasound in children is governed by very strict rules. An example of how helpful it can be is the case of a young girl with an aortic isthmus stenosis. The two-and-a-half-year-old had been fitted with an aortic stent, but suffered a partial tear of the external iliac artery when the sheath was withdrawn. After surgery, using a patch, a large haematoma developed in the abdomen which was to be punc-

tured with the help of ultrasound, because the CT scan showed no bleeding. Only the contrast ultrasound image actually showed a small leak in the patch.

Consequently, no puncture was carried out, but immediate surgery to remove the haematoma and revise the patch. 'Although the use of contrast medium in this case was off-label,' says Clevert, 'the medical team were within their rights to utilise CEUS, as its use paid off for the patient 100%.'

Not all problems can be solved by using ultrasound, however. As a rule, the following applies: The better an organ can be visualised with ultrasound the better the results of contrast-enhanced ultrasound will be. If visualising the liver is difficult because of meteorism contrast-enhanced ultrasound also cannot rule out liver lesions. 'The better the basic settings, the cleaner the use of ultrasound, the better the result achieved with CEUS. Obviously you also need a good system for this,' he points out. 'We can't expect the same performance from a mid-range scanner as from a high-end system. In other words, we have to adapt our expectations to the equipment!'

Clevert is pleased that Samsung has now penetrated the established market for high-end equipment.

Most companies have decades of experience and can adapt their systems to customer specifications. 'If you want to compete in this market your system must have an edge over those offered by the competition. As a new player in this market, Samsung had to make large investments to get to the point where a scanner is not just a 'nice to have tool' but diagnostically innovative. But the company is gaining ground, aided by its fast development of software and the openness towards suggestions from clinicians,' Clevert enthuses.

Within clinical routine, Samsung's RS80A with Prestige mostly wins over in workflow. The company is at an advantage here, due to its extensive experience with monitors in the consumer sector. The touchscreen is of a particularly large, convenient size and clearly arranged. An additional, flexible, portable touchscreen, which could be used to present the day's caseload during meetings, would be beneficial, but would basically be a 'nice to have tool.'

What is really essential for high-end equipment is good, contrast enhanced ultrasound, whilst compression and shear wave elastography are now also a 'must', and so is image fusion, and the RS80A with Prestige offers all of this. 'There are

penetrate the blood-brain barrier and treat tumours. There are powerful synergies here.'

The future of ultrasound imaging

It can take 20 years from the discovery of such headline-making achievements until they come into routine clinical practice, cautioned Professor Michel Tanter from the advanced engineering College of Physics and Chemistry in Paris, France. He then launched into a presentation of yet another break-through potential for microbubbles in super resolution ultrasound medical imaging.

Building on work that won a Nobel Prize for Chemistry in 2014, his group has demonstrated the first ultrasound-based microscopic imaging technique that allows clinicians to non-invasively look deep inside living tissue for the early detection of cancer tumours or cardiovascular and neurologic pathologies.

'This is a true revolution and we are only at the beginning,' Tanter said. 'Yet we can be sure the technique will become more powerful with even faster image processing capabilities emerging and smaller, enhanced microbubbles.'

Bubbles outside the body

Microbubbles are popping up in multiple fields outside medicine as scientists apply them to solving problems as diverse as cleaning tools, and even endodontic treatment, to smoothing the powerful churning of turbines to produce electricity.

Professor Michel Versluis is from the Physical and Medical Acoustics Physics of Fluids Group at the University of Twente, in the Netherlands, which is part of a consortium of two other universities that recently won funding of €36 million from the Dutch government to advance their work.

Using ultra-fast optical imaging of microbubbles, his group hopes to increase the efficiency of cata-

lytic reactions to optimise processes for various energy and materials sources, such as fossil fuels, biomass and solar energy. Mohamed Farhat, Senior Scientist at the Polytechnic University in Lausanne, Switzerland is investigating the potential of microbubbles to fix problems caused by cavitation in hydraulic machines. 'Bubbles produced in industrial flow processes cause nothing but problems for noise and vibration, due to cavitation.

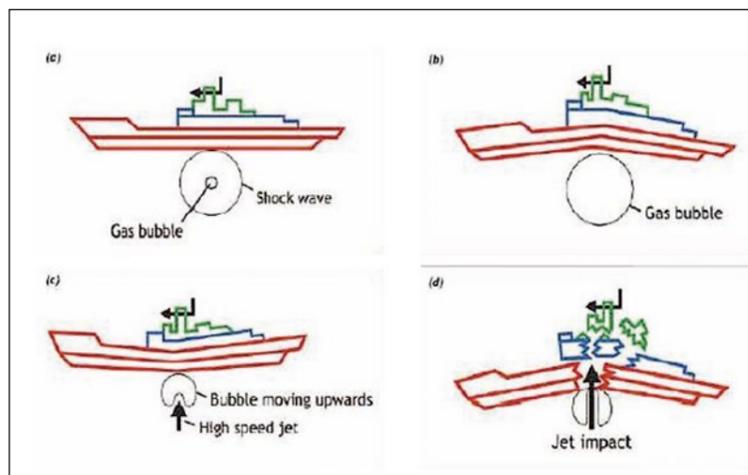
'Turbines crack, plants are shut down and the costs of these effects are very high. What we are asking is how we can turn these bad bubbles into good bubbles?' he said.

New horizon

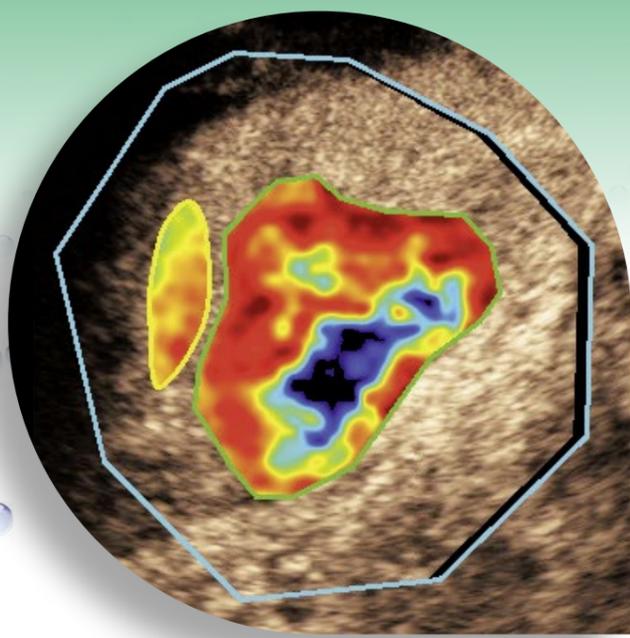
Dr Peter Frinking, Senior Scientist at Bracco Research in Geneva, agreed that it took 20 years for the current generation of microbubbles to reach the point where today they are advancing science as well as enhancing diagnostics and patient therapies.

'What will be the next big thing? What does all this mean for the next generation of microbubbles?' he asked the scientists.

'We need a greater understanding of the acoustics, the biology and the potential applications, which is what this symposium has been all about. We may not be able to predict the future, but we certainly want to be ready for it,' Frinking concluded.



How to sink a ship



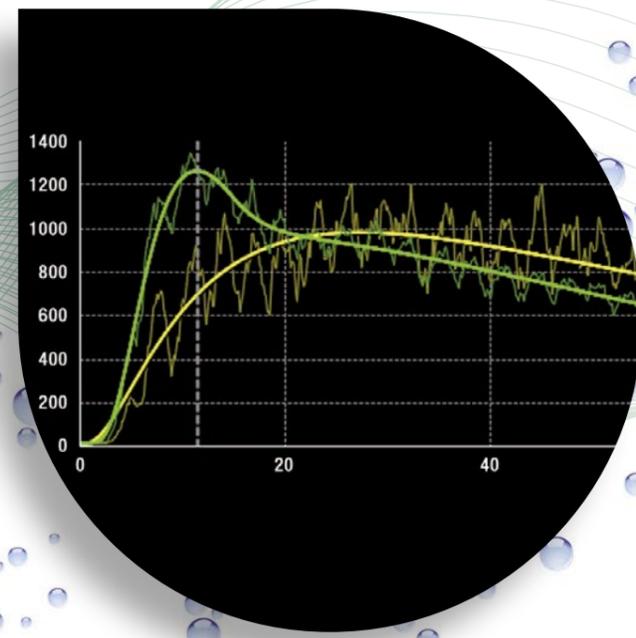
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Berlin-born Professor Dirk-André Clevert began his career at the MRI Diagnostics Institute Westend in that city and in the Department for Internal Medicine at the Waldkrankenhaus Granssee. He then worked as a specialist registrar in the Department of Radiology at Passau Hospital for three years. In 2003, he moved to Munich and joined the newly founded (2004) Interdisciplinary Centre for Ultrasound at the Grosshadern Campus, University Hospital Munich. The centre coordinates all ultrasound activities in the hospital. As course director and congress president, he organises numerous national and international ultrasound courses and congresses. On the 80th founding anniversary of the Medical Faculty of Tbilisi State Medical University, Clevert, as head of the Interdisciplinary Ultrasound Centre, was awarded an honorary doctorate.

some very exciting questions for ultrasound and there is still a way to go to fulfil all the demands from high-end users,' Clevert concludes. 'But Samsung is definitely heading in the right direction.'

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Ultrasound can reveal different types of shock in trauma

Resuscitation: E-FAST or CT?

Ultrasound examinations are considered cost-efficient, fast and effective. The E-FAST (Extended-Focused Assessment with Sonography for Trauma) is a standardised examination used in accident & emergency medicine worldwide. The procedure helps to diagnose internal bleeding and organ damage in severely injured patients in the resuscitation room and, in some regions, even during emergency transport to the hospital, gaining valuable time for the primary care of these patients. [AWMF Register No. 012/019].

'Apart from haemorrhagic shock there are other forms of traumatic shock which are just as life-threatening,' explains Dr Dieter von Ow, Assistant Director of the Central Accident & Emergency Department at the Cantonal Hospital St. Gallen.

Although haemorrhagic shock is common there are also non-haemorrhagic types of shock, such as tension pneumothorax, cardiac tamponade or severe paraplegia with neurogenic shock.

With tension pneumothorax, a valve mechanism, particularly during artificial ventilation, increases pressure in the pleural cavity so much that the venous return to the heart is impaired, resulting in circulatory shock.

A cardiac tamponade leads to direct compression of the cardiac chamber and thus a reduction of the stroke volume. Cardiac tamponade is relatively rare, but fatal if not diagnosed. These two types of shock are not caused by blood loss,' von Ow explains, 'but by the aforementioned, direct increases in pressure in the mediastinum or the pericardium. Not rarely do the latter two types of shock also occur combined with



Tension/pneumothorax: (lack of lung sliding in the moving image), lack of comet tail artefacts and distinct reverberations ('lines')



Normal findings: (lung sliding, moving image), comet tail artefacts (on the left in the image)



(Massive) haemothorax: Fluid (blood, hypoechoic) between diaphragm and thoracic wall, with an atelectatic lung section ('half moon') 'swimming' inside



Pericardial effusion: Fluid (blood, hypoechoic) between the pericardial sac and the heart suggested compression of the right ventricle (tamponade)



Haematoperitoneum: Fluid (blood, hypoechoic) between kidney and liver, i.e. in the Morison's pouch



Haematoperitoneum: Fluid (blood, hypoechoic) in the lesser pelvis, with the uterus and full bladder, separated by the bladder wall (on the right in image) 'swimming' inside

blood loss, which leads to severe impairment of the patient's circulation and requires fast treatment.'

Each patient with potential multiple injuries or uncertain injuries admitted to the Central Accident and Emergency Department at the Cantonal Hospital St. Gallen is examined with the E-FAST procedure. 'This involves assessing the thoracic cavity, or the pleural cavity respectively, in so-called sectional planes, ventrally and from the side towards the armpits. This provides clues as to the potential presence of tension pneumothorax or haemothorax. The

subcostal plane makes it possible to diagnose a cardiac tamponade. A tension pneumothorax, a massive haemothorax or a cardiac tamponade require immediate release of air, or blood respectively, by the insertion of the appropriate drainage in the resuscitation room.'

Responses to responders and non-responders

The peritoneal cavity is also examined for the presence of free fluid via sectional planes from the sides, toward the abdomen and in planes directed towards the lesser pelvis.

to be stabilised in the resuscitation room – the so-called 'responders' or 'transient responders' – are immediately given a polytrauma CT scan and, depending on the results of this scan, the further (surgical) strategy is then determined,' von Ow explains. [klinikarzt 2012; 41 (1): 26-30]

This point-of-care ultrasound is handled in a very similar way in many trauma centres and is always carried out at the beginning of treatment. It is conducted by specialists in emergency medicine, traumatologists, anaesthetists or radiologists in the resuscitation room, requires six sectional planes to ensure a safe diagnosis and takes only a few minutes.

It answers a small number of specific questions: Is it a tension pneumothorax? A cardiac tamponade? Is there fluid – i.e. blood – in one of the three large cavities, i.e. the thorax, abdomen or pelvis? (The ability to differentiate between these types of shock requires conducting 50-100 such bedside examinations under supervision).

The results of the examination either lead to life-saving intervention in the resuscitation room, or they support the life-saving triage decision 'Emergency surgery or polytrauma CT'.

In other words, 'E-FAST can save lives,' von Ow is convinced. Current data from large trauma registers confirm this statement. When multiple trauma patients are given a CT scan without being assessed via this system beforehand, this does not improve their chances of survival [The Lancet 2016; 388: 673-83]

The parenchymal organs, the liver, spleen and kidneys can also be assessed via contrast medium ultra-

Finding shocking and potentially fatal bleeding in the lesser pelvis is not always easy because dissecting aneurysms are not always easy to detect retroperitoneally. Severely injured patients in persistent shock, i.e. so-called 'non-responders' defined by unchanged blood pressure readings below 80mmHg, despite the administration of fluid, who have large blood loss in the thorax, abdomen or pelvis diagnosed via the E-FAST procedure must undergo emergency surgery without delay.

Multiple trauma patients who need

Mobile digital X-ray units for hospitals a

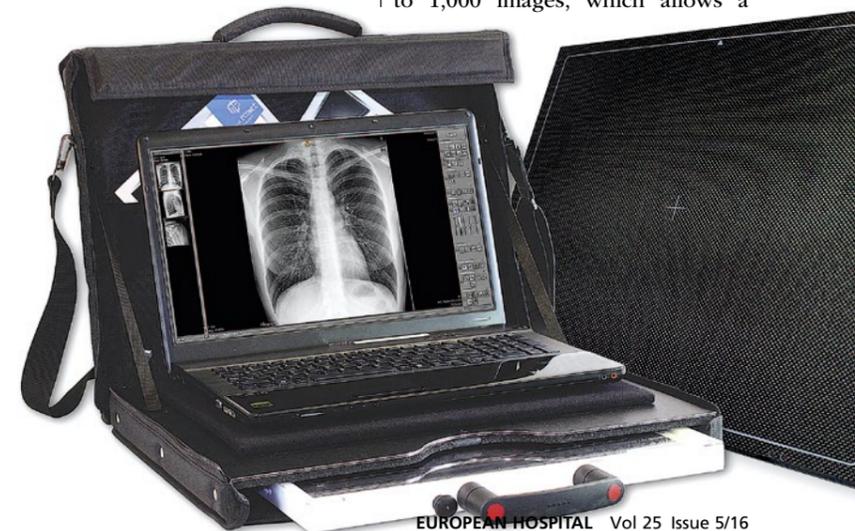
Wireless radiography the move

With clients worldwide, the 20-year-old imaging and digital radiography solutions firm medical ECONET provides mobile radiography systems to hospitals, ambulance and mobile home care services, military clinics in conflict zones, as well as medical facilities on sea-going vessels.

With clients worldwide, the 20-year-old imaging and digital radiography solutions firm medical ECONET provides mobile radiography systems to hospitals, ambulance and mobile home care services, military clinics in conflict zones, as well as medical facilities on sea-going vessels.

To that end, the firm's radiography solutions are equipped with a

unique hybrid-powered technology. The firm describes its mobile X-ray system POX-100BT as 'an ideological designed foldable device, which allows the user to work completely without any cables and without dependence to electricity due to its integrated high-performance Lithium-ion battery. With one full charge it is possible to make up to 1,000 images, which allows a



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EUSOBI 2016 Annual Scientific Meeting breast imaging session



Internal Medicine and Intensive Care specialist **Dieter von Ow** is also qualified in clinical emergency medicine at SGNOR (Swiss Society for Accident and Emergency Medicine). He is a course instructor and tutor for abdominal ultrasound and point-of-care ultrasound (basic emergency ultrasound, echocardiography, thoracic and musculoskeletal ultrasound), as well as course director/instructor for Advanced Trauma Life Support (ATLS) American College of Surgeons and Advanced Cardiovascular Life Support (ACLS), American Heart Association. He has worked in the Central Accident and Emergency Department at the Cantonal Hospital St. Gallen for 15 years, where he is currently Assistant Director. This is Eastern Switzerland's main hospital providing maximum care for around 40,000 patients annually. As one of the Swiss Trauma Centres it is included in the national trauma register.

sound instead of CT, he explains. However, there are only few radiographers experienced enough to carry out the procedure on trauma patients.

Nevertheless, it does significantly reduce the potentially carcinogenic radiation exposure from CT scans and other radiological examinations, particularly for children and adolescents, given that the radiation exposure following relevant trauma exceeds the average annual terrestrial exposure per patient 15-30 times.

nd more...

graphy on

complete unrestricted workflow in many different scenarios without any external power source.

The POX-100BT is quickly installable and smooth to move, due to the big inflated wheels. The power output of 5 kW enables examinations of all human body parts without limitations.'

The firm's wireless Digital Radiography (DR) detector meX+1417WCC has an imaging size of 36 x 43 centimetres – beneficial when mobile.

'Due to the wireless file transfer and automatic exposure detection (AED) of the detector, the user can work in a most comfortable way without any disturbing cables.

With only 3kg weight, the flat panel is very easy to handle and provides brilliant image quality within few seconds after the exposure. The equipped meX+ Image Acquisition Software allows the optimisation and full diagnosis of images and external provision by a patient's CD, e-mail or tele-radiography.'

The best image results are achieved by combining a UHD resolution notebook, the device manufacturer advises.

Highest mobility helped by a light-weight carrying bag for the DR system

'The best way to screen'

The European Society of Breast Imaging (ESOBI) promotes high quality breast imaging across Europe by developing education and training, encouraging research and promoting guidelines and standards. This year's meeting (23-24 September) was held in collaboration with the French Society La Société d'Imagerie de la Femme (SIFEM) and drew around 600 radiologists. The event included a two-day course on breast magnetic resonance imaging (MRI). Jane MacDougall reports.

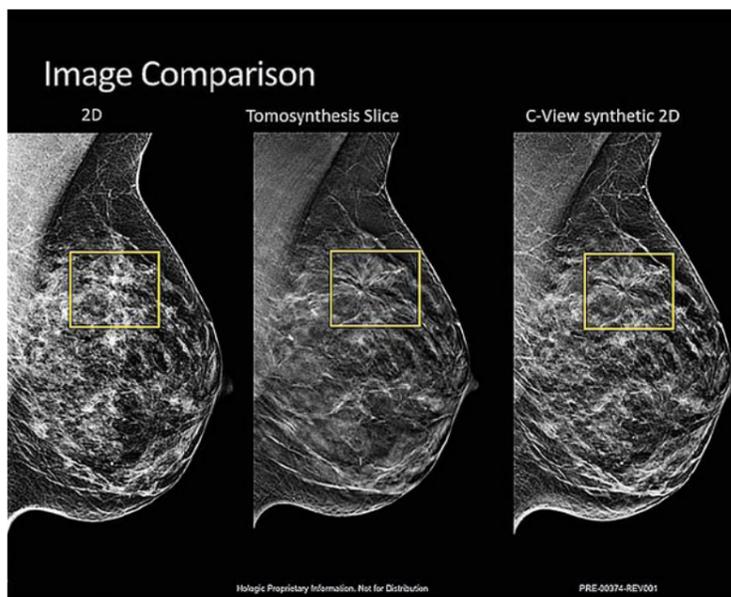
Aiming to balance the latest in cutting-edge science with everyday clinical practice, this year's ESOBI meeting featured a session entitled the 'The best way to screen'. A timely debate in light of the new draft proposal for European guidelines for breast cancer screening and diagnosis that is open for feedback and also when ESOBI are promoting their latest publication 'Statement in favour of breast screening'.

Nationwide screening programmes result in substantial mortality reductions

Screening with mammography alone is a cost-effective way to save lives. Throughout Europe a substantial reduction in mortality from breast cancer can be seen in those countries that have implemented nationwide screening programmes. Interestingly, the shift from analogue to digital between 2005 and 2010 led to improved results and showed that more high-risk tumours are now detected by mammography.

Of course, there remain drawbacks with mammography screening, such as false positives and over diagnosis. However, so far no other modality has proven to save lives and no information is available regarding the aggressiveness of tumours detected by other modalities, for example the positive predictive value of ultrasound is substantially lower and quality control (operator dependent) is difficult.

For these reasons screening with mammography alone is still the gold standard for population-based



DBT with FFDM demonstrates increased rates in cancer detection compared with FFDM alone. Image comparison between 2-D, tomosynthesis and C-view synthetic 2-D

screening programmes.

Nevertheless, even screening with full-field digital mammography (FFDM) fails to detect 15-30% of cancers and in women with dense breasts, approximately 7% of the 50-70-year-old population, sensitivity for 2-D mammography can be as low as 58%.

Digital Breast Tomosynthesis (DBT), a 3-D digital mammography system, is a promising tool for improving screening in these women. After X-ray acquisition of a series of 2-D images (projections), reconstruction of the breast is done

at different heights above the detector. Current DBT systems are commercialised by five different manufacturers and are routinely used in radiology centres and in several countries, the technique has approval for screening and diagnostics.

Comparison of DBT with FFDM favours DBT

DBT has the potential to improve cancer detection rates with only a small increase in radiation dose. Retrospective reading studies comparing DBT with FFDM have shown improvement in both sensitivity and

specificity with DBT. Diagnostic accuracy appears to be largely independent of breast density although benefit appears greater in women with denser breasts. Results are less clear regarding the detection of microcalcification and most studies have found little improvement over 2-D mammography in the detection of ductal carcinoma in situ (DCIS).

Used together in prospective screening studies, DBT with FFDM has demonstrated increased rates in cancer detection compared with FFDM alone. A reduction in false-positive recall rates has also been shown in nearly all studies.

Several DBT issues must now be resolved

Screening with the addition of DBT would approximately double the radiation dose received; but a simulated FFDM image can be generated from a DBT scan. The combination of simulated FFDM images and DBT is being evaluated within several studies and some positive results have been published.

However, before this becomes a realistic proposition for widespread screening programmes several issues around DBT need to be resolved, not least the wide range of totally different characteristics in the machines (angular range, scanning angle, filter/target combination, tube motion, etc.), and the use of different reconstruction methods: filtered back projection or iterative reconstruction.

Also, the additional reading time, the large IT storage, connectivity problems and over diagnosis of low grade cancers will all need to be correctly modelled to obtain cost-effectiveness similar to that of current screening if the addition of DBT is to become a way to improve breast cancer screening

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Armored Cable

'Dr Computer' may aid intelligent lung

In imaging diagnostics computers are taking over – well, not quite, but they might soon play an important role, according to Professor Hans-Ulrich Kauczor, Medical Director of the Clinic of Diagnostic and Interventional Radiology at University Hospital Heidelberg. Meeting with European Hospital, he discussed an EU-funded project to assess malignancy in pulmonary nodules and its implications for the radiologist's profession.

Asked whether the computerised assessment of pulmonary nodules is on the way, Kauczor confirmed: 'Colleagues from Oxford and Groningen and our team are indeed working on using computer algorithms based on CT images to detect and characterise pulmonary nodules. We submitted the proposal for EU funding and received a favourable response.'

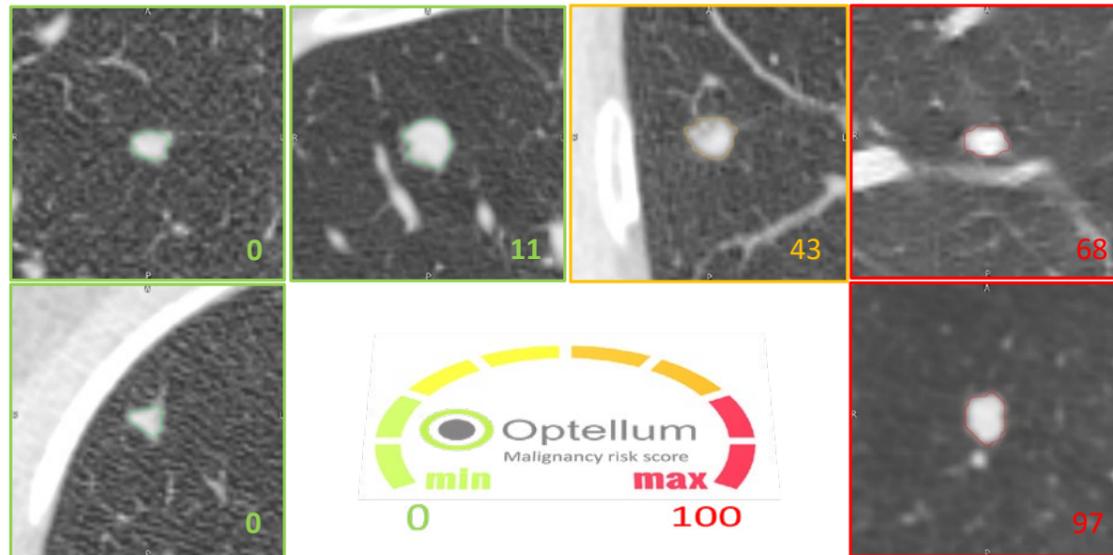
'Thus, we expect the project, to be known as 'Lucinda', to start next year. It aims to develop a method for intelligent lung cancer diagnosis.'

'The task at hand is to validate the performance of an algorithm, which was initiated by a team at Oxford University Hospital headed by Fergus Gleeson and then further developed by Optellum, a spin-off company. Preliminary tests and publications are promising.'

'The idea is to use Big Data and machine learning. We'll have to assess whether the programme also works with images from different sources, such as different scanners, and with different slice thicknesses

and different reconstruction algorithms. We will contribute a set of CT images of the lung with a validated diagnosis of pulmonary nodules. The images were acquired in our

Heidelberg lung cancer screening cohort LUSI and in clinical routine at the Thorax Clinic of Heidelberg University Hospital. The colleagues from Groningen will draw on the



Pulmonary nodule malignancy scores predicted by a research prototype of the system. The images show axial slices of a Chest CT volume (5cm x 5cm screenshot centered on the nodule of interest).

Nelson cohort, a Dutch-Belgian lung cancer screening cohort.

'We aim to collect 2,000 data sets. We hope, when reading the 2001st data set, the algorithm will tell with 90 percent specificity whether the tumour is malignant or benign.'

Could a computer alone come p with a diagnosis?

'The computer will facilitate our

work – and that reflects the fact that there are fewer and fewer experts in this highly specialised area. As radiologists, we want the machine to do the groundwork but we'll remain the ones to make the final decision.'

'If the radiologist turns into a mere report generator, the discipline will lose its charm and the profession will lose its attraction. Nobody wants to be in a profession where the mark of distinction is the ability to read 1,000 images or more a day. To diagnose more patients with more images in less time – that is not going to improve quality.'

'Machine learning is a promising option for the radiologist to get help with the basics. But in the end the machine cannot evaluate the results it generates. The role of the radiologist will move towards placing the results in a context, evaluating and communicating them.'

'For example, an algorithm that can reliably assess a pulmonary nodule can be used very well for screening purposes. The primary aim is to find out whether we are dealing with a malignant tumour or whether the lesion might become malignant. If a lesion is found to be malignant it is the task of the radiologist to refer the patient for further diagnostic work-up and therapy

Research: Measuring gas exchange in MRI

A revolution in lung function diagnosis

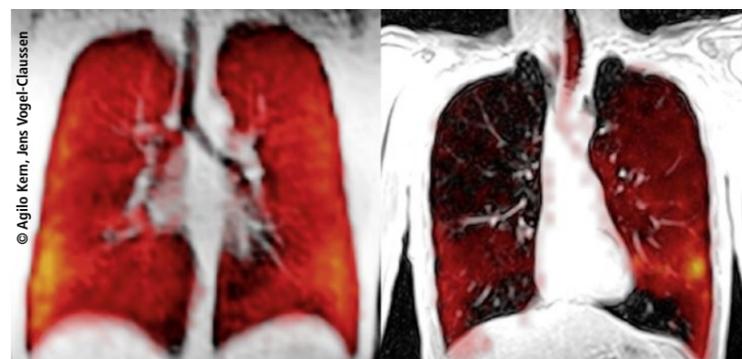
Since lung diseases tend to be complex, imaging is a crucial diagnostic tool. While computed tomography has become the standard modality, which is frequently used outside hospital settings, specialised MRI diagnostics remains the preserve of large university medical centres. Until recently, lung MRI was considered a difficult procedure. Now, new methods enable lung function measuring, particularly gas exchange, in the MR scanner. With his team, Professor Frank Wacker, Director of the Institute of Diagnostic and Interventional Radiology at the Medical School Hanover, focuses on this research. Marcel Rasch reports.

Usually, a general practitioner diagnoses pulmonary hypertension, rather than a hospital-based specialist. The patient is referred to a pneumologist who charts the further course of action, which might include a surgical intervention or balloon pulmonary angioplasty (BAP). Imaging is a pillar of the diagnostic work-up, but CT has turned out to be inadequate to detect so-called web stenosis in the pulmonary vessels. This is where MRI comes in, which today offers local lung function assessment supplementing CT.

A milestone in pulmonary research

'We are still charting unknown territory,' Wacker concedes, 'but the research results are promising.' He and his team, headed by Professor Jens Vogel-Claussen at the Institute of Diagnostic and Interventional Radiology, are exploring potential uses of MRI in lung function diagnostics. 'MRI diagnostics now offers a method to not only assess tissue change and morphology but also the function of different lung sections and to quantify blood flow,' Wacker explains. 'Beyond knowing how much blood is passing through which lung section we need to assess ventilation and gas exchange.'

The fact that gas exchange can be measured in MRI is nothing short of a revolution in lung function diagnostics. 'We use hyperpolarised xenon to visualise the gas exchange,' he explains. In a first step the xenon

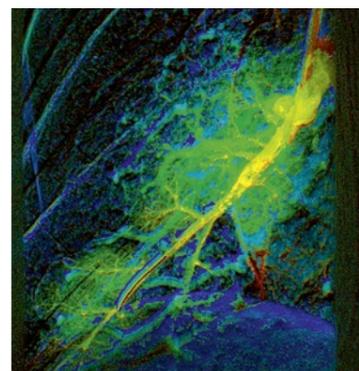


Normal case with Xenon

has to be processed in a polariser for the MRI scanner to achieve high SNR. The Hanover Medical School works closely with the Fraunhofer Institute ITEM in Hanover to show the path of the gas and the speed of diffusion from the alveoli into the blood circulation.

'Basically we use two gases: fluorine shows the distribution of tidal air. However, this gas does not penetrate the alveoli – which can be an advantage as well as a drawback,' Wacker points out.

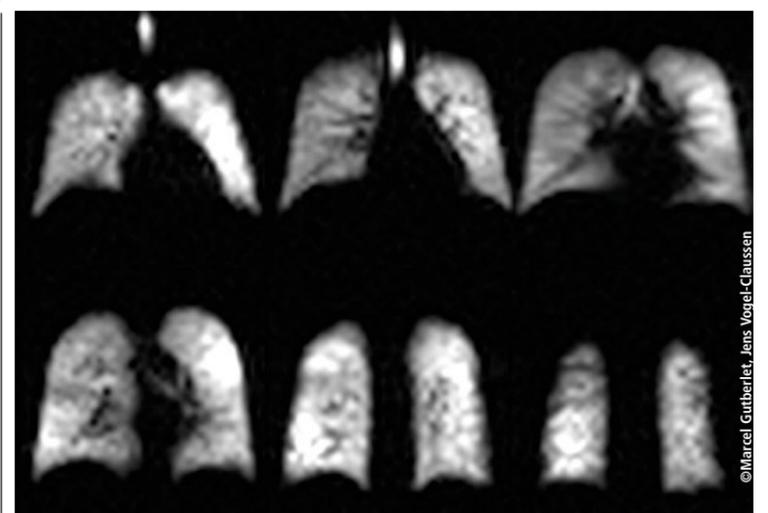
The gas stays in the lungs rather than being absorbed by the body, which allows precise steady state assessment. 'In MRI, fluorine can be selectively stimulated. But, to examine the passage across a membrane we need xenon since, unlike fluorine, it does not remain in the alveoli but enters the blood stream through the membrane and can be measured in the MRI scanner,'



Wacker says of this milestone in pulmonary research.

Benchmarking

Nevertheless, much research remains to be done in order to define 'normal' values. 'Obviously, we are progressing systematically,' he emphasises. 'We look at study participants, COPD patients and others and, based on known pathologies, we try to establish what a



On the left, 19F MRI lung shots of a healthy person with normal regional breathing and on the right a COPD patients with significantly impaired breathing

'typical' MR image is supposed to look like.'

Hanover offers an excellent environment for intensive and meticulous research. 'We are lucky to have on board Professor Tobias Welte, an internationally renowned pneumologist, and Professor Marius Hoepfer, a specialist on lung hypertension. Moreover, we have access to the largest lung transplantation programme, which was established by Professor Axel Haverich. Moreover, the teams in pneumology, HTG surgery and radiology are doing world-class research,' he adds.

Not to forget the team at the previously mentioned ITEM, which also focuses on pulmonary research. All lung specialists in Hanover are part of the research network 'Biomedical Research in Endstage and Obstructive Lung Disease, Hanover (BREATH)', one of the five sites of the German Centre for Lung

Research (DZL). Wacker calls it 'an ideal set-up which offers perfect synergies'.

Japanese researchers are pioneering treatment approaches, particularly for chronic thromboembolic pulmonary hypertension (CTEPH), triggered inter alia by the fact that Japanese physicians, for cultural reasons, tend to avoid open thoracic surgery and prefer balloon pulmonary angioplasty. 'This method is an option for many patients who are considered non-operable,' Wacker points out. 'Initial results at the Hanover Medical School are rather promising.'

While stenoses are usually calcifications in the large arteries of the pelvis or the thigh, CTEPH is characterised by web-like membranes in the pulmonary arteries. Both, the working group headed by Professor Meyer in radiology, and the one headed by Professor

ct and characterise pulmonary nodules

ing cancer diagnoses



Since 2008 Hans-Ulrich Kauczor has been full Professor and Chairman of Radiology at the University of Heidelberg and Medical Director of Diagnostic and Interventional Radiology at the Heidelberg University Hospital. He has also been Principal Investigator of the Translational Lung Research Centre in Heidelberg (TLRC) and, since 2012, the German Centre for Lung Research (DZL).

along the clinical path.

'The clinical situation, however, is fraught with a number of challenges. Let's say the patient is sick and presents with different comorbidities. Then we have to evaluate the images in their clinical context, help the referring physician to determine the right therapy and follow up on it. Machine learning systems cannot

handle this type of complexity in the clinical environment.'

Will the profession now known as 'radiologist' change

'We have to move from volume-based to value-based radiology. The American College of Radiology faces this challenge with its Imaging 3.0 strategy, which aims to integrate contact with the patient and his or

her family much more tightly in the work of the radiologist. I consider this to be of utmost importance.

'Our very dense and optimised workflows confuse the patient: he sees five physicians who give him four different explanations.

'The radiologist's clinical services should be performed reliably and the relevant information should be provided to all parties involved in a

comprehensible and usable manner. Not every physician in the treatment context has to actually see the patient.

'As far as I'm concerned, the challenge for the profession "radiologist" and the advanced training is not to consider computers a black box, but to master them. We have to know our systems. What input do we provide and what the output is going to be? How do we acquire images? Which protocol am I to use and why? What is the function of contrast media? To what extent can I rely on the results? This is the core

of the discipline: interpretation and decision making. 'We cannot ignore the trend towards Big Data – and we don't want to. As radiologists we pioneered the integration of IT and PACS and have proven to be innovative.

'Unfortunately, during the past five years we have lost ground. I think that is a big mistake. We are, and should remain, the experts when it comes to image data, networking, interpretation, decision-making and associations. This is where we have to look for a sustainable definition of our role.'



agnostics



After graduating in medicine in Tübingen, Germany, Professor Frank Wacker trained in radiology and neuro-radiology at Charité, Berlin, where he was senior physician and subsequently appointed Deputy Clinic Director of Charité, Campus Benjamin Franklin. He held several visiting professorships in the USA, enabling him to pursue clinical and research projects, at the University Hospital of Case Western Reserve University in Cleveland and John Hopkins Hospital in Baltimore. A university professor for many years, in 2010 Wacker was appointed Director of the Institute of Diagnostic and Interventional Radiology at Hanover Medical School. He holds a Level 2 and a training certification for interventional-radiological procedures from the German Society for Interventional Radiology (DeGIR).

Hoepfer in pneumology, underline the importance of visualising the stenosis prior to the intervention. The imaging data are then used to guide balloon pulmonary angioplasty and increase safety of the procedure. Wacker:

'During balloon pulmonary angioplasty the webs are blown up, so to speak, to improve blood flow. We are currently analysing the success of this therapy approach.'



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Microsoft lifts French software into cloud computing to teach machines how to read tumour 'fingerprints'

Turning a CT scan into a virtual biopsy

John Brosky reports

Cloud-based mining of medical images will transform clinical radiology the same way that online access to genetic data has transformed clinical biology, according to Frederik Brag, the CEO of Median Technologies.

Microsoft Corporation believes he is right and this summer created a joint initiative with Median to integrate its IBIOPSY software into that company's Azure cloud platform to provide clinicians with capabilities for analysing medical images for cancer diagnosis and treatment.

'Using Big Data analytics we can now do what we call decoding images, breaking them down to identify unique signatures or fingerprints that correspond to a specific kind of cancer,' Brag told *European Hospital*. 'It's like performing an imaging biopsy and this is especially powerful. A regular biopsy gives you partial information at best about a piece of tissue to be analysed.'

'We can look at the whole image of an organ and any tumours. We can sequence the image, decode it and correlate our results to a biopsy report.'

Since 2002, Median has steadily improved its software algorithms for detecting, identifying and tracking changes in tumours. Over the

past three years the company has emerged from its headquarters in Sophia-Antipolic, France, to become a leading provider of automated image analytics for pharmaceutical companies conducting clinical trials.

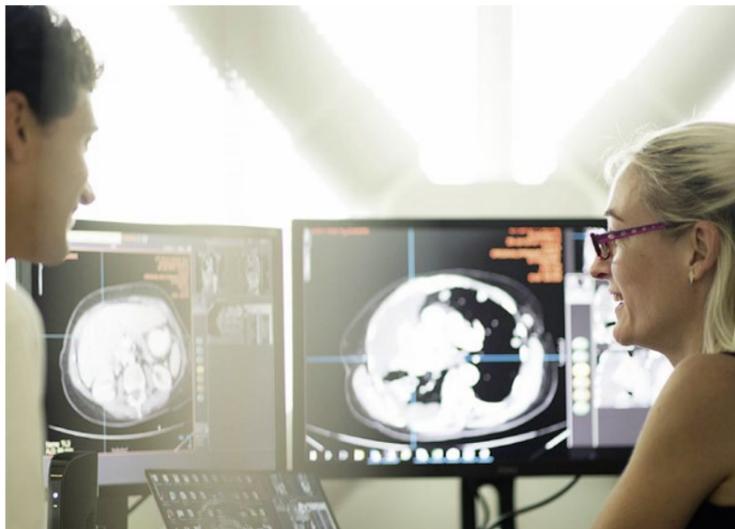
Medical imaging is the established standard of care in oncology and is used to determine if a new drug is having any impact on a patient.

During the course of a clinical trial, a single patient will undergo up to eight imaging examinations to determine whether a lesion is stable, if it is continuing to grow, or if it is getting smaller.

He estimates imaging represents almost 15 percent of oncology clinical trial budgets, with each drug company spending up to €50 million per year for imaging interpretation and analysis, creating a global market valued at €1 billion annually.

Previously, a dedicated team of radiologists would gather the massive batch of images for each clinical trial and would manually read, interpret and report on the outcomes.

'They are selling radiology services at a premium to the drug companies,' said Brag. 'These central lab teams do not have the capacity for understanding exactly the type of tumour they are looking at, they are not equipped to do quantitative imaging and in 40 percent of the cases two



Monitoring changes to a pulmonary lesion measured by RECIST (Response Evaluation Criteria In Solid Tumours) criteria using the Lesion Management Solution from Median Technologies

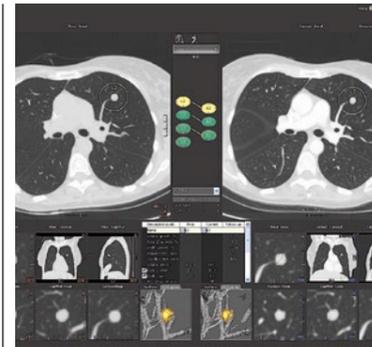
radiologists will report two different assessments of how the same patient is responding to treatment.

'We use software to standardise the interpretation and make results reproducible, automatically detecting cancer lesions and measuring them in 3-D to get the full volume of a specific tumour and extract much more meaningful information that gives a pharma group a much better understanding of how a patient

is responding to treatment,' he said.

Today, there is a new breed of technology moving into this space, driven by companies like Microsoft, as well as Google, Amazon and IBM. 'It's a combination of capabilities coming from different fields that are dramatically changing the landscape.'

'There are faster processors today. We do billions of computations on one image and we can now index the data in a totally different way.



Just two years ago it took us two weeks to do the analysis on just one patient. Today, we can do it in less than one minute. This means the analytics can be applied in a much wider space,' Brag pointed out.

Bernard Ourghanlian, Chief Technology Officer with Microsoft said, 'by taking advantage of the Microsoft Azure cloud platform, IBIOPSY will provide faster imaging and health data analysis and will accelerate the discovery and delivery of new biomarkers for cancer diagnosis and treatment monitoring.'

By identifying the unique visual characteristics of tumours, Ibiopsy is progressively extracting biomarkers of disease from medical images. 'This is at the core of the Microsoft-Median Technologies Precision Medicine Project,' Brag confirmed.

'Big Data computing and analytics will allow efficient processing and analysis of imaging biomarkers, which is essential for early detection of cancer and monitoring of new targeted cancer treatments. Our collaboration with Microsoft will allow us to deliver these solutions into routine clinical practice on a global scale on the Azure cloud computing platform.'

Automation helps radiologists

The billions of medical images taken and diagnoses made every year across the globe are as varied in quality, detail and structure as the situations in which they are obtained. Contrary to popular belief the huge majority of medical data is available only in unstructured form which considerably impairs efficiency in the healthcare system. Peter Aulbach, Siemens Healthineers' Business Manager for CT in Germany, explains how these data – if they were analysed systematically – could provide clinical insights and help improve patient care.

Many research projects worldwide focus on machine learning: software that is able to automatically answer clinical questions such as the assessment of medical images. How will such algorithms impact the healthcare system?

That is a very exciting field of research which will dramatically alter the healthcare landscape. As a company we are observing a few trends that are most likely here to stay, such

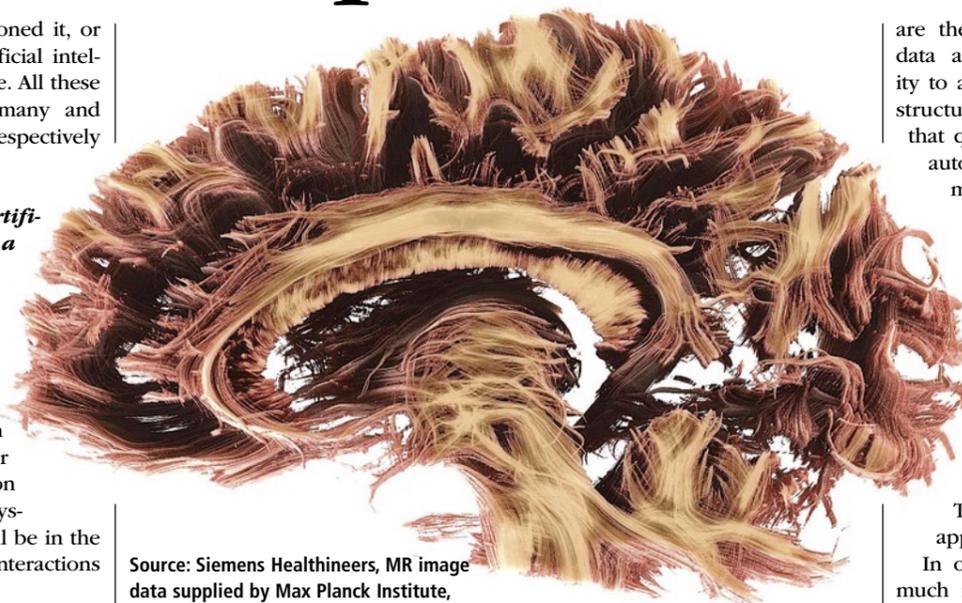
as automation, you mentioned it, or the increasing role of artificial intelligence – AI – in healthcare. All these topics aim to generate many and above all comparable, respectively reproducible data.

In which areas will artificial intelligence play a role?

AI is primarily important in decision support systems. We talk about artificial intelligence when an algorithm or a software programme can learn and suggest a diagnosis or even a therapy based on evidence. The more the system learns the better it will be in the future and the fewer user interactions are required.

That is a prospect many people find scary.

Maybe. One thing, though, is certain: We cannot work without computers anymore! Computers are far



Source: Siemens Healthineers, MR image data supplied by Max Planck Institute, Leipzig, Germany

superior to human beings when it comes to rational intelligence and they do make better decisions. That's a fact. Ideally, we manage to align the machine's rational intelligence with the emotional skills that characterize us as human beings. The population is ageing and we need more and more trained people who are able to diagnose, interpret and treat. But the number of these people does not increase exponentially; quite on the contrary, the number of experts is decreasing, widening the gap in our system. That also holds true for radiologists who are inundated with slice images and are having an

increasingly hard time catching up. With DNA sequencing, functional MRI and CI imaging and many other digital developments, the data floods will continue to rise.

This is where radiology is facing another problem: We still lack standardisation and structured storing of image and diagnostic data. Amassing data won't help if these data are not structured. Huge unstructured data pools are useless. Today, most of the data obtained gather dust so to speak in the modalities; only 2 percent are archived for later use.

What would a solution look like?

We consider so-called DICOM structured reports to be key. These reports

are the wheel-barrow with which data are carried from the modality to a Big Data form. Widely used structured reporting will ensure that quantified data are transferred automatically from the imaging modalities to the PACS – and thus are converted into a Big Data-usable form.

In the USA, for example, by law every TV show has to be transformed into text. The texts can be analysed using algorithms. Thus you can find out how often the words Clinton or Trump or any other word were used in a certain period of time. That's a quintessential Big Data application.

In our field, however, things are much more complicated. While we do have many video and image data, they are of little value since they are not categorised. The structured report is the key to this treasure trove. Templates will allow us to make huge steps forward, since templates are configurable, but even more importantly – if DICOM and HL7 can agree on a single standard – they will contain the acquired image data as well as the AHA and ACC guidelines and transfer these templates to the PACS.

You aim to automate sequences, protocols and post-processing. Won't that make the radiologist obsolete?

No, we don't want to make the radiologist obsolete. Quite on the con-



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Reading everything, forgetting nothing is elementary to 'Dr' Watson

Big data takes a big brain

Agfa HealthCare aims to tap the IBM-Watson super-computer to bring big data analytics to medical imaging, John Brosky reports

Because no one can know everything, radiologists often consult with colleagues to deliver a diagnosis. Soon they may be able to call upon the world's smartest computer, a learning machine that reads everything and forgets nothing.

This summer Agfa HealthCare announced it had joined the Watson Health Medical Imaging Collaborative built around IBM's Watson, the famously brainy super-computer that regularly defeats grand masters at chess, wins every television game show contest and has even created 65 new gourmet recipes.

Turning from fun and games, Watson entered the medical field by consuming libraries and journals and one year ago digested 315 billion medical imaging data points and 90 million unique records following IBM's acquisition of Merge Healthcare's database. Watson today is able to read medical images, which IBM estimates account for 90% of all medical data today.

To find out how Watson can be harnessed to help deliver information useful for patient care, European Hospital spoke with



Peter Aulbach, Siemens Healthineers' Business Manager for CT and Radiation Oncology

trary: we want to make all data available which the medical expert needs to get a full picture of the situation. Going forward, the radiologist will be an information broker who leverages the modalities, which are high performance systems generating reproducible results, with little standard deviation and in a structured way. He no longer will have to sit in front of a screen and plough through reams of slices to arrive at a conclusion.

This is where radiomics comes in. In the US, there is a company with this name that owns a patent on the analysis of oncological image data from MRI and CT scanners and already offers pattern recognition.

The company does nothing but look for structures in segmented images. It identifies patterns which are compared to previously defined master data in order to describe patient groups. The number of such procedures will increase – and this is something we want to support. But in the end it is the radiologist who will continue to make the clinically and therapeutically relevant decisions.

James Jay, the Global Vice President and General Manager for Imaging IT at Agfa Healthcare.

Why is Agfa investing in the Watson Health Medical Imaging Collaborative?

James Jay: 'It's about us trying to find a way to deliver the most powerful analytics capabilities in the world to users on our Enterprise Imaging platform. So they can tap into Watson as part of the work they already do today. That's why IBM asked us to be part of this. They realise that, as powerful as Watson may be, the last thing healthcare professionals want is to see yet another computer added to their office! They already have electronic medical record systems, medication administration systems, imaging systems such as PACS.

'Agfa's Enterprise Imaging platform becomes a great vehicle to deliver Watson's powerful capabilities as part of their daily work.'

Coming down from the general idea of cloud computing, what can Watson do to help healthcare professionals?

'One of the challenges with Watson is that it is capable of doing anything. The difficult question is to ask what do we want it to do. Ultimately, we want to approach hospitals to say, specifically, that we can help with their work in a specific area, built on specific real-



world use cases. An example would be in lung cancer. Watson studied lung cancer at Memorial Sloan-Kettering Cancer Center where it not only integrated lung images; it also learned the specific pathologies around lung cancer. In a hospital we can help improve the analysis of the pixel data in the CT studies of the lung, to run comparative analytics, perhaps to identify secondary findings. For example, a clinical team may be looking at the liver while a Watson-capable system might see a reason to also go look at images of the patient's lungs and find a nodule. The radiologist would not have spotted this, because the doctor's request was to look at the liver.

There is software that can detect cancer. What is the difference between medical software analysis and Watson analytics?

'You can teach software to recognise specific patterns in a medical image, but then that software will only be capable of looking for the specific patterns that have been coded. Watson is adaptive. It is a learning platform that uses data sets to make itself smarter when it looks at new images in the future. Watson reach-

es into a massive reference database with an enormous machine-learning capability. It can tap health records, radiology or pathology reports, doctors' notes, medical journals, clinical care guidelines and published outcomes studies all at once. There are amazing things that can be done with a machine that learns!'

Agfa believes that Watson can help find 'invisible, unstructured imaging data'. Where is this invisible imaging data?

'There are several levels of information in every medical image, the patient information linked to the image, which is structured but only used for indexing the image. There is a radiology report that is not structured. And then there is the pixel information contained in the image itself.

'The patient information can be used for much more than indexing. Data taken only from the image, without going to the patient medical record, includes the patient's age, sex, height and weight, for example. This can be used to create comparative perspectives, to link that patient to a specific patient population and enrich demographic information.

A vice president with Agfa Healthcare James Jay is the General Manager for Imaging IT and serves as a member of the company's Board of Directors for its USA operations. He is also the holder of five patents for the functions behind displaying and comparing image studies, as well as enhancing workflow. With deep experience in developing medical device software and working in a regulated environment, James is actively involved in numerous healthcare IT associations and organisations

'The unstructured radiology report can be ingested by a learning machine using textual tools and turned into a wealth of information that can be mined. And, finally, there is an underlying analysis of the pixel data. The image the radiologist sees has been examined for a specific request, but is not examined in conjunction with a wider comparative study that may show the pixel pattern represent something different when analysed from this different perspective.'

Does Agfa want to become the interface between man and machine, between doctors and Watson?

'To deliver big data analytics to clinicians in the future, you have to already be in front of them today, part of their daily work. They are not going to add more and more systems to look at; they want to do the opposite, to work on fewer and fewer systems.

'Right now we have the attention of more than 10,000 users to whom we can deliver advanced capabilities through our Enterprise Imaging platform. This becomes a vehicle to aggregate the capabilities of very smart people out there developing analytics and other services helpful for healthcare professionals, our users.

'So, yes, Agfa will become the aggregator of analytics for physicians and clinicians through the interface on the Enterprise Imaging platform.'

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50 shades of grey in hybrid imaging

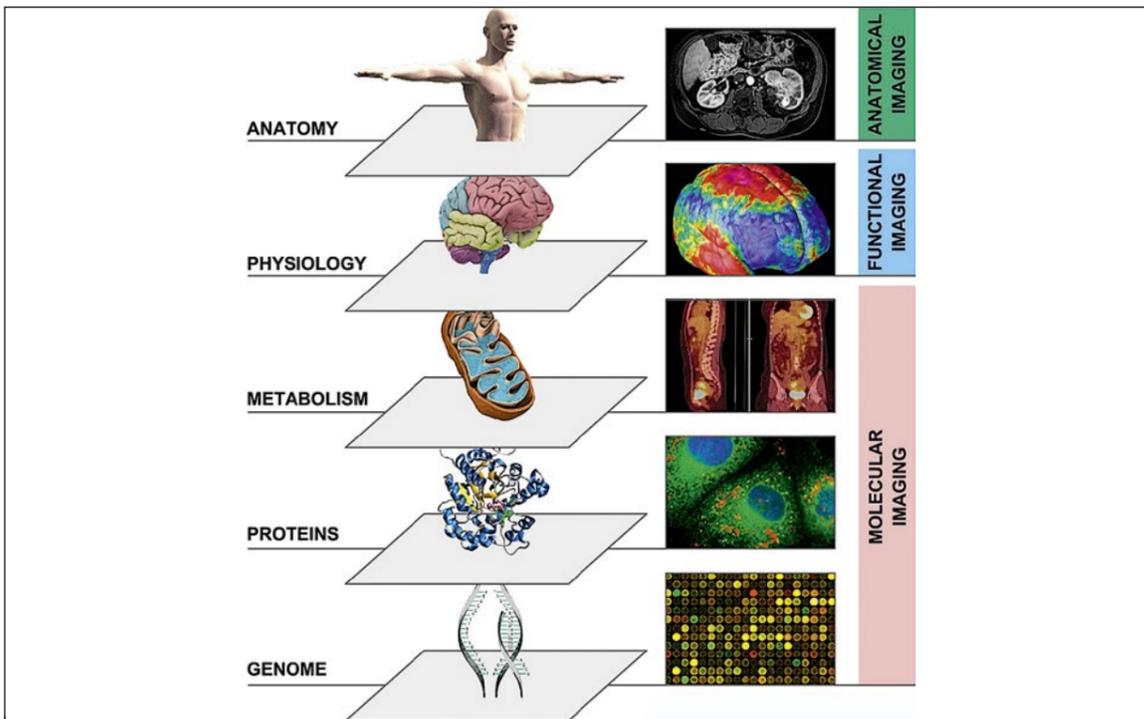
Fusion imaging will create a multi-modality monster for radiology groups that already struggle to deal with data from dual-modality hybrid systems, John Brosky reports

Hybrid imaging is growing so big it is gaining a new name: multi-parametric imaging. You might see it as converging streams of digital data from genomics, metabolomics and proteomics. Or on a bad day it may seem more like the multiple heads of a hydra rising up to gobble every gigabyte of patient data they can grasp.

But that comes later. Because Thomas Beyer is a Professor of Physics of Medical Imaging at the Medical University Vienna, he likes to take a step back for a running start before leaping into the future.

As the Deputy Head of the Centre for Medical Physics and Biomedical Engineering at the Medical University, Beyer presented an overview of the growth of hybrid imaging at a well-attended course for the European School of Radiology.

In the beginning there was hard-



ware, said Beyer, a wide range of imaging modalities from X-ray, scintigraphy, to computed tomog-

Multi-parametric imaging of tumour biology

raphy (CT) to ultrasound (US) and magnetic resonance imaging (MRI). The origin of many of these modalities was around the 1950's, with the developmental approaches being mainly independent. The combination of anatomical and functional imaging was first attempted when clinicians, as early as the 1960s, used a pen to mark body contours around scintigrams, or else adjusting overlays of printouts on light tables to co-register images from the nuclear medicine and radiology examina-

tions. The fusion of images, using software that is familiar to us today, really took off in the 1990s with the digital availability of images and increase in computing power.

Beyer explains that the problem with both software and manual fusion is that they only work for limited axial ranges that largely exclude image co-registration between the two modalities being used. For this reason, hardware fusion has emerged, where two imaging modalities are physically combined within one gantry so that two co-registered exams can be taken as a single examination protocol.

The three clinically relevant hybrid imaging examinations combining dual modalities are SPECT/CT, PET/CT, and PET/MRI. While PET/CT and SPECT/CT came out about the same time, commercially available around 2000 and 2001, SPECT/CT has not enjoyed the same level of adoption, he said, estimating that for every SPECT/CT system installed around the world there are five PET/CT systems.

PET/MR was introduced in 2006 and commercially available in 2011, he said; yet there are barely 120 systems installed worldwide to date. 'It remains hotly debated whether PET/MR is a clinical or a research machine because there is not yet any data supporting a clinical application with a proven clinical benefit,' said Beyer. 'Clinical PET/MR is a bit like the iPad, something everyone wants, that no one needs, but once you have it you are actually quite happy using it.'

Like a late child in the family, PET/MR is challenged by the prior existence of PET/CT. Johannes Czernin, who leads the Nuclear Medicine group at the University of California Los Angeles, once said PET/CT is a technological evolution that led to a medical revolution. Beyer finds that PET/MR is something like a medical evolution based on a technical revolution.

A further evolution to multi-parametric imaging seems inevitable, where swelling databases of digital images and ever-faster computer processing will combine other imaging modalities, biopsy data, patient predispositions from genetic information and biologic data.

'This rises to the level of Big Data, where some companies, like Microsoft and Google, are already thinking about how they can put all of this together,' he noted.

His concern about the rush to multi-parametric diagnosis is that clinicians are still struggling with the flood of information from dual-modality platforms. 'We will need to



A small X-ray system on large all-terrain wheels

The go anywhere medical a

Developed entirely by the Rostock firm Oehm und Rehbein (OR) technology, the fully digital Amadeo M mini X-ray system incorporates a sophisticated design that reduces components to the most essential, functional operating elements. The device is therefore particularly suitable for portable use and can easily be transported due to its low weight (approximately 68 kg) and compact build, the manufacturer points out. 'The new system is attractive wherever it's not possible to move patients to a hospital for diagnostic radiology. Areas of application are first aid services, home care, nursing homes, medically oriented aid organisations, military purposes and for ships or oil rigs.'

Additionally, the lightweight system can be pulled easily over steps

and obstacles and swivelled in all directions – a huge advantage in confined spaces and elevators, the firm adds. 'The X-ray system is stable and does not tip over on uneven terrain. Its large, all-terrain wheels permit effortless movement. The Amadeo M mini includes all necessary compo-

nents of a functional system: X-ray detector, X-ray generator and image processing workstation. The latter is delivered with a globally proven software package dicompACS DX-R, which includes a convenient X-ray positioning guide for fine adjustment (except the AX-version).'

Oehm und Rehbein GmbH (also known as OR Technology) will be demonstrating the firm's products at Medica 2016, in Dusseldorf, Germany. 14–17 November. Booth E35. Hall 10.

Details: www.or-technology.com.



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A shift from qualitative to quantitative imaging and Big Data



Thomas Beyer is Professor of Physics of Medical Imaging at the Medical University, Vienna.

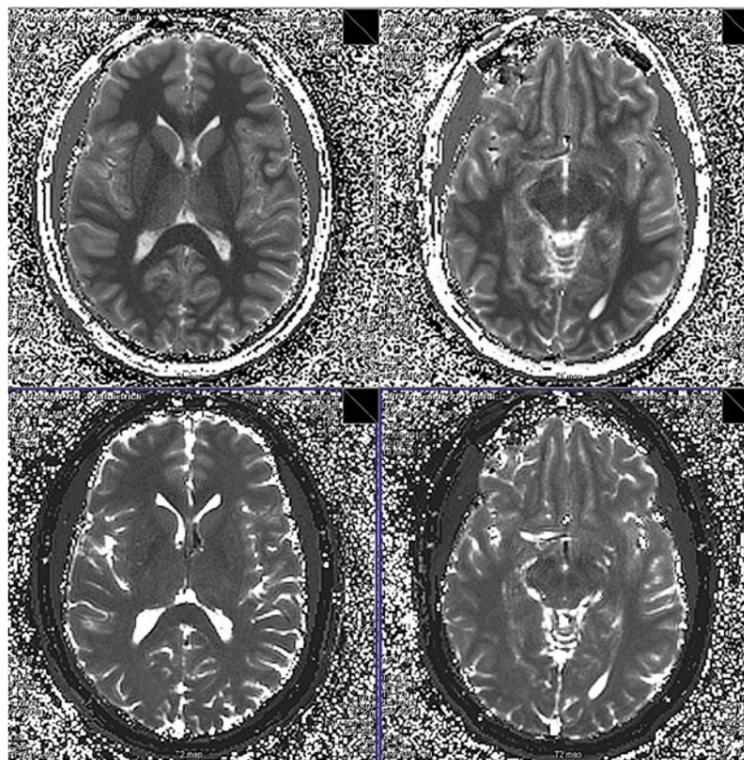
invest in Big Data and to integrate all patient data available, yet we need first to bring the existing hybrid modalities to an efficient and proper use, to get a handle on the data we already have.

'My own perspective is that, whilst the big vendors provide big platforms to acquire the images, they really fall short of expectations regarding the means they provide to handle this imaging data. PET/MR is a prime example. There are 50 shades of grey information acquired that combine with four-dimensional PET information. There is a plethora of data, yet the software tools provided are too inefficient to extract all the information that is in there,' Beyer said. 'It's like acquiring a Porsche but you can only run it in first gear.'

Before more information begins to fall from cloud computing, 'There needs to be an investment in software platforms that allow us to extract more information,' he believes. 'We need to find ways to combine this with the complementary information, different levels of information about metabolics, proteins, genomics. We need to bring in specialists beyond nuclear medicine and radiology.'

'It's time for us to bury our internal conflicts and open up to embrace other specialties. That becomes critical if this is going to fly,' he said. 'Rather than asking: What can dual-modality imaging do for me? We should ask: What can I do with dual-modality imaging for others?'

Radiologists will become computer technicians



T-1 and T-2 mapping, wherein the T-1 maps (top row) and T-2 maps (bottom row) were obtained by means of MR Fingerprinting

'Magnetic resonance imaging is a very dynamic field,' declared Professor Siegfried Trattnig, head of the Centre of Excellence for High Field MRI in the Department of Biomedical Imaging and Image-guided Therapy, at Vienna Medical University. Indeed, this September, two mega trends emphasised by Trattnig – the shift from qualitative to quantitative imaging and Big Data – dominated the 33rd Annual Scientific Meeting of the European Society for Magnetic Resonance in Medicine and Biology (ESMRMB) in Vienna, for which he is Local Organising Committee Chair.

On conventional MR images lightness and darkness don't correspond with absolute values but merely serve to help the radiologist make a diagnosis based on the respective contrasts. Modern MRI procedures, such as MR fingerprinting, however, can precisely quantify the three basic MRI parameters (T1 relaxation timings, T2 relaxation timings and proton density). This data can be used to generate maps which, at first glance, look like conventional contrast images, but which are capable of far more: they contain accurate measurements. Each pixel of a T1 map for instance corresponds with an exact T1 measurement. 'This way the differences between pathological and healthy tissue can be clearly established. When monitoring the progress of treatment, for instance, it is possible to see how the measurements change, and to assess the efficiency of the treatment,' Trattnig explains.

Until recently, the generation of a T1 or T2 map took about 10 to 15 minutes – too long for clinical routine applications. The new technologies make T1 or T2 mapping possible in one to two minutes. Furthermore, there is now the respective software that evaluates the maps at high speed. 'This makes it really interesting for clinical routine,' he points out. As the maps always contain the entire MRI infor-

analysing the large amounts of data.

Trattnig also expects the emergence of new findings from the comparison of imaging data with data from genomics, proteomics or metabolomics.

Big Data for instance is also essential for the ever more important research into dementia, he explains. 'We need a very large control group to classify the normal aging process

and to differentiate it from the early stages of dementia.'

These developments will lead to changes in practice for radiologists. 'The radiologist will no longer make a diagnosis in the conventional way by standing in front of contrast images but will become more like a computer technician,' Trattnig believes.

Radiologists will have to acquire in-depth knowledge of the new procedures to keep up with the developments ahead.



Siegfried Trattnig is professor for radiology with a particular focus on High Field MRI at the Vienna's Medical University, where he has been Medical Director of the High Field MRI research scanner since 2000 and also heads the High Field MRI Centre (HFMR) since its foundation in 2003. The professor is a member of over 50 committees in all important international, radiological, orthopaedic and MRI societies. Since its formation two years ago Trattnig has also been chaired the European Imaging Biomarker Alliance (EIBALL).

mation the conventional contrast images can be synthetically generated retrospectively. 'There is no need to examine the patient with different sequences. A one-off measurement of the T1 and T2 values suffices,' Trattnig explains.

All these examinations generate vast amounts of data. As a representative from the industry reported at the ESMRMB Congress, Siemens alone has so many MRI scanners in use that 33,300 patients are being examined per hour worldwide. 'If you have the respective tools, there is the opportunity to extract diagnostic information from this vast pool of data, which you cannot gain from individual examinations alone,' says Trattnig.

Software based on machine learning can discover whether certain image data point towards certain diseases; it can discover correlations as yet unknown, or confirm suspected correlations respectively by



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Extending intra-operative radiotherapy to breast treatments

Dutch centre of excellence a dedicated device

Patients with locally advanced rectal cancer have been treated with intra-operative radiotherapy (IORT) for over twenty years. Partly due to this type of radiation, survival rates in a group of patients considered to have inoperable cancer changed dramatically from five to 70 percent.

The top clinical and referral centre Catharina Hospital in Eindhoven is one of two hospitals in the Netherlands where patients with rectal or breast cancer can be treated with IORT. Recently, the hospital installed a Mobetron – the first mobile, self-shielded, electron linear accelerator to deliver IORT to cancer patients during surgery.

The manufacturer notes that the device brings safe, reliable radiation to the operating theatre without the

need for costly shielding renovations or retrofits.

Self-developed adaptation

'In our breast centre we used all possible methods of treatment, except IORT,' explained breast cancer surgeon Yvonne van Riet, at the Catherina Cancer Institute. 'We were interested in this technique, but it's not a toy and should be safe. We started to use it in 2012 because of the outcomes of the first randomised study on IORT use on breast cancer patients, by

Professor Umberto Veronesi at the Italian Cancer Institute in Milan.'

The breast cancer treatment is focused on irradiating the area where the tumour tissue (radical) has been removed and to do this



to the least possible surrounding healthy tissue. In Italy and in other centres, they stick the tissue together to determine the irradiation site. We realised that there could be a more accurate way, so, with our radiotherapy department, we developed a screen plate that we place in the breast muscle after tumour removal. This protects the underlying ribs, lungs, and also the left side of the heart from the applied radiation.

Then the mammary gland tissue to be irradiated is stuck together; the irradiation tube is positioned and coupled with the irradiation unit. In this way you can determine very precisely where you need to irradiate without affecting the surrounding tissue.'

New device choice

The old linear accelerator used for IORT needed replacement. 'The

Mobetron meets all our requirements. It is user-friendly and safer because there is less radiation leakage into the environment. It's not only an investment in equipment, but also in the possibility to continue the treatment and help even more women,' said radiation oncologist Jeltsje Cnossen, explaining the institute's choice.

'For IORT you need specially equipped operating rooms with extra thick walls,' van Riet added. 'And, very important: you need a team of experienced specialists, surgeons and radiation oncologists who seamlessly respond to each other.'

Therefore IORT cannot be applied in every hospital. Currently, in the Netherlands, it is provided in only the Catharina Cancer Institute and the Medical Centre Haaglanden, in The Hague.

Less harmful than regular radiation

IORT is meant for women of 60 years and older with diagnosed breast cancer and a tumour no more than 2 centimetres in size. In addition, it should be sensitive to female hormones and there should be no malignant cells detected in the sentinel lymph node.

'The treatment lasts one and a half hours,' van Riet said. 'After the tumour removal by surgeons the area is treated only once with a higher dose of radiation than in external radiation. The patient is discharged from hospital the same



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Vienna: The 13th Forum on Hospital Management in Vienna

Cost cutting cancer drugs

Report: Michael Krassnitzer

How to cut the high cost of cancer drugs engendered high interest at the recent Forum on Hospital Management held in Vienna. 'When it comes to cancer drugs, we have a daily dilemma with effectiveness and financial viability,' laments Professor Gabriela Kornek, Medical Director at Vienna's General Hospital (AKH). Whilst there have been huge advances in cancer treatment over recent years, the price of cancer drugs has risen just as much as the number of cancer patients.

More and more people affected are aged above 50 years – the age where the probability of developing cancer increases significantly. The survival time after a cancer diagnosis has risen considerably. In Austria, for example, 60% of cancer patients survive for more than five years. Patients only used to receive treatment for six months, but nowadays cancer treatment can last for a year or, if the tumour is inoperable, for life. This means an increasing number of people receive cancer drugs.

At the same time, costs have exploded. Nowadays, drugs for colon cancer treatment cost €122,000 for

22 months, whereas a few years ago this was just €600 for 12 months. 'The cost of treatment has risen by two hundred-fold,' Kornek emphasises. In 1985 a melanoma diagnosis was more or less a death sentence. Today, up to 22% of patients can actually be cured. However, the combination of drugs required to achieve this amounts to €125,000 over two years. 'The cost of the leading 58 drugs per year of life gained was €54,000 in 1995; in 2013 it was €207,000,' Kornek points out. At Vienna's AKH, 43 percent of all the money spent on drugs is allocated to cancer drugs.

How might this expenditure be cut? At the Forum, Kornek listed a number of possibilities – including the inclusion of patients in clinical studies. By including 18 patients at the in the AKH Novo-Study, which examined the effects of Nivolumab on lung cancer patients, melanoma patients and those with renal cell carcinoma, the hospital could save €2.8 million in 2013/14.

Hospitals can also cut costs for effective but very expensive drugs by negotiating with drug manufacturers. The so-called Capping Model, where the cost of drugs per patient

is capped, is one example. The annual dose of Bevacizumab for a colon cancer patient weighing 70kg is 9,100 milligram per year; for other types of tumours the dose required for patients of the same weight is twice as high. Due to pressure from customers, the drugs manufacturer is now offering Bevacizumab 'free of charge' for amounts from 10,000 milligrams per year, i.e. costs are capped at around €55,000.

Another cost saving route is the 'pay for performance' model. One feature of modern cancer drugs is that, dependent on the tumour genome; they are effective for certain patients but not others. The manufacturer of Bortezomib, licensed to treat multiple myeloma, has negotiated the following deal with the National Health Service: The NHS initially pays for four treatment cycles. If the patient responds to treatment the NHS will bear the cost of further treatment; however, if the patient does not respond the manufacturer will refund the cost of the first four cycles.

Oncologists have also thought of a decision aide for the use of expensive cancer drugs: The Magnitude of Clinical Benefit Scale



Viennese native Professor Gabriela Kornek MD is Medical Director at Vienna General Hospital (AKH), one of Europe's largest hospitals. A specialist in Haemato-oncology, she is also Deputy Head of the Department for Oncology at the University Clinic for Internal Medicine I at the AKH, and also programme director for ear, nose and throat tumours and head of the Cancer School at the Vienna's Comprehensive Cancer Centre. The professor has published 164 scientific articles in peer-reviewed journals, along with a specialist book plus further book contributions. She is also a member of numerous scientific associations.

of the European Society for Medical Oncology (ESMO) assesses the actual clinical benefit of tumour treatments. This includes, for instance, the stipulation that a cure has priority over delay and death, or that direct endpoints (overall survival, quality of life) have priority over surrogate parameters (progression-free survival, response rate). 'After approval of a new drug, the ESMO Committee evaluates it. Drugs with the highest classification are included in the ESMO guidelines,' Kornek explains. 'They receive full support for absorption of costs in the European committees.'

adopts

day and doesn't have to return for radiotherapy for three weeks, five days a week. This means less stress for the woman concerned."

Effective

Figures from both hospitals show that the treatment is effective and the number of relapses is not higher or smaller than the treatment with external radiation. 'In 2017 we will have used this technique for five years,' van Riet said. 'Then we can



Surgeon Dr Yvonne van Riet has worked at the Catharina Hospital since 2002. Following training as a general surgeon she specialized in cancer surgery, on a broad level. From 2005, she has focused on breast cancer. Along with colleagues she established the use of a small radioactive rod (125-iodine seed) on breast abnormalities so that, in just one procedure, a breast tumour can be removed. The technique is now used in the Netherlands. Van Riet also chairs the Mamma Centre at Catharina Hospital and is President of the hospital's Quality Commission for Oncology



After gaining a BSc in Medicine (Groningen Univ.) Dr Jeltsje Cnossen, trained as a radiation oncologist at the University Medical Centre Utrecht and gained a PhD at the University of Amsterdam, and MSc in Epidemiology at the EMGO Institute. Today, she is a radiotherapist at the Catharina Hospital in Eindhoven, focusing on gynaecological, oesophageal and colon tumours, intraoperative radiotherapy (IORT), brachytherapy and palliation.

measure the results of the first group of about 250 to 300 patients and review the longer-term results.'

'The general trend is that treatments for cancer are becoming more individual,' Cnossen pointed out. 'Meaning not to treat all patients with the same brush, but to look at what is possibly most effective and the least burdensome. The Mobetron will certainly contribute to that goal.'

Known for cancer and cardiovascular disease treatments, the Catherine Cancer Institute acts as a Centre of Excellence and last resort in terms of, inter alia, rectal cancer, breast cancer, peritoneal metastases of colorectal cancer, cardiac arrhythmias, valvular interventions and oesophageal disorders. ■

Fighting cancer with sticky nanoparticles

A team of researchers at Yale found that a treatment using bio-adhesive nanoparticles loaded with a potent chemotherapy drug proved more effective and less toxic than conventional treatments for gynaecological cancer. The results of the work, led by Professor Mark Saltzman at the Yale School of Engineering and Applied Science and professor Alessandro Santin at the Yale School of Medicine, appeared Sept. 19 in the Proceedings of the National Academy of Sciences.

The nanoparticles are loaded with a drug known as epothilone B (EB) and injected into the peritoneal space, the fluid of the abdominal cavity. EB has been used in clinical trials to target tumour cells resistant to conventional chemotherapy agents. The drug proved effective in these trials, but severe side effects caused by the drug's high toxicity prevented further use.

The Yale Cancer Center researchers' treatment significantly reduces the drug's toxicity by encasing it in a nanoparticle that gradually releases the drug in high concentration at the cancer site. The problem with conventional nanoparticles, though, is that they are cleared from the target region too quickly to have much of an effect due to their small size, note the scientists. 'The challenge was to find a way to use that drug, which is very effective if you can keep it in the right place for a long enough period,' said Saltzman, the Goizueta Foundation Professor of Biomedical

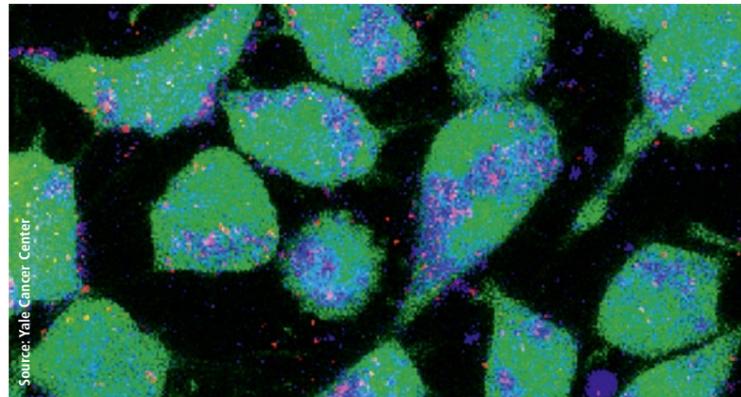


Image of cancer cells (green) taking up fluorescently labelled nanoparticles (red), demonstrating the possibility of more efficient delivery of traditional cancer drugs.

and Chemical Engineering. To that end, the Yale team developed nanoparticles covered with aldehyde groups, which chemically adhered to mesothelial cells in the abdominal cavity when injected into the peritoneum. Tested on mice with human tumours growing in their abdominal regions, the bio-adhesive nanoparticles stayed in place for at least 24 hours. Non-adhesive nanoparticles injected into control mice began to leave the abdominal cavity after five minutes. Sixty percent of the mice receiving the treatment with the bio-adhesive nanoparticles survived for four months — a significant improvement over mice in the control groups, where 10% or fewer lived as long.

By localising the delivery of the drug, Santin said, they both decreased the toxicity of the drug

and increased its effectiveness. This treatment could be particularly beneficial to patients with later stages of ovarian and uterine cancer, which is extremely difficult to treat due to how the cancer spreads in the peritoneal region, he said. 'They've been treated with surgery and chemotherapy and are now resistant to any standard treatment, and we've shown that this agent can be effective,' said Santin, professor of obstetrics, gynaecology, and reproductive sciences, and research team leader of the Gynaecologic Oncology Programme at Smilow Cancer Hospital at Yale New Haven. In future studies, Saltzman said, they may 'tune' the nanoparticles' properties. For instance, they can adjust the adhesiveness of the particles, and how quickly the particles release the drugs at the target site. ■

A new breast imaging system is on the horizon

Radiowave breast imaging technology

A new radiowave breast imaging technology will become available before 2016 ends, according to Micrima, the Bristol-based breast imaging company and developer of a CE Mark approved radiowave breast imaging system. The firm has successfully gained a new financing round of £2.6 million, which will support accelerated development of its patented Maria technology. This aims to enable breast screening to become safer, more comfortable and more accessible to a larger proportion of the global female population, the manufacturer reports. 'The com-

pany intends to start the commercialisation at the end of the year.'

Roy Johnson, Micrima's Executive Chairman: 'The problem is that many tumours are not discovered early enough, largely due to the difficulty in discriminating between cancers and dense tissue using current imaging technology.'

'Using harmless radiowaves, the Maria imaging system is capable of detecting tumours in dense tissue and allows routine and repeated scanning without any of the safety or comfort concerns associated with X-ray mammography.'

The funding comes at an exciting period of significant progress for Micrima, with the first clinical data from Maria presented at the European Congress of Radiology last March.

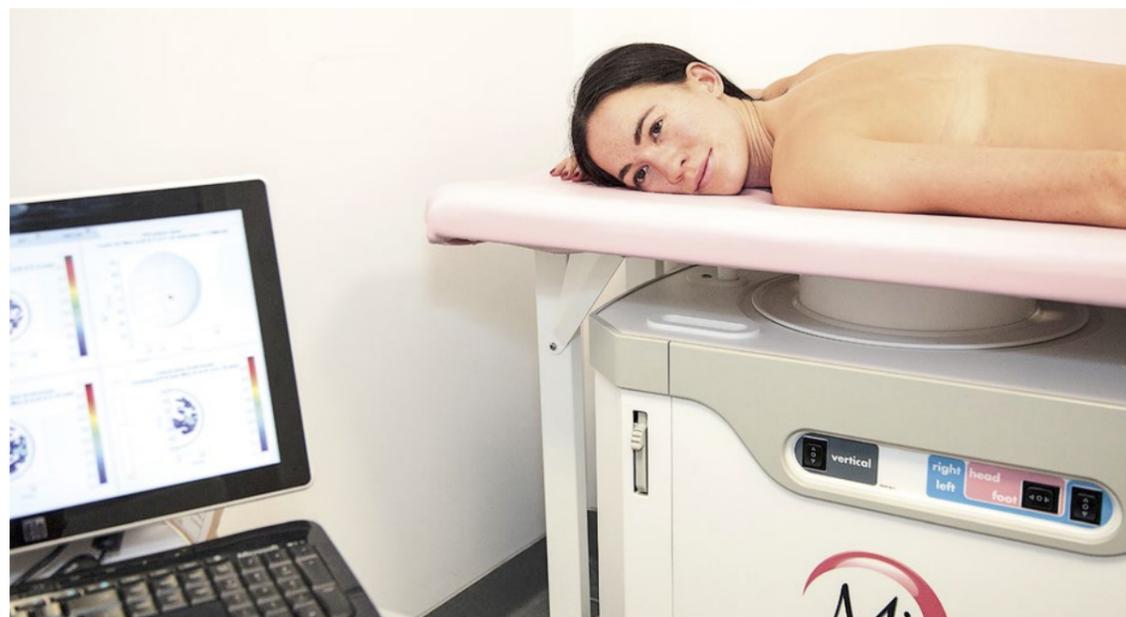
The latest results from current multi-site clinical trials were presented at Symposium Mammographicum in Liverpool in July.

The Journal of Medical Imaging has also accepted a paper reporting the pre-CE Mark clinical trial for publication.

The Maria radiowave breast imaging technology was initially pio-

neered at the University of Bristol, in the UK. It received European regulatory approval in 2015 and is

currently deployed in clinical trials based at several breast cancer imaging centres throughout the UK. ■



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Vienna peaks in breast cancer research

Study reveals therapy-induced osteoporosis can drop by 50%

Report: Michael Krassnitzer

'Today Vienna is one of the top addresses with regard to breast cancer research,' Professor Michael Gnant proudly reports – and he certainly knows what he is talking about. The surgeon is Director of the University Clinic for Surgery at the Vienna's Medical University, Deputy Director of the University's Comprehensive Cancer Centre (CCC) and President of ABCSG, the Austrian Breast & Colorectal Cancer Study Group. During the past few months, all three institutions published stunning research results in *The Lancet*.

ABCSG-18 demonstrates that, in patients with early hormone-receptor positive breast cancer, the administration of the human monoclonal antibody denosumab, along with the standard endocrine therapy, can reduce by 50 percent therapy-induced osteoporosis, a long-term side effect. Subcutaneous administration of 60 mg denosumab, twice a year, basically halves the risk of fractures without side effects.

Moreover, the study results show that bone density in the spine increased by ten percent, in the hip by eight percent and in the femoral neck by six percent.

'These results are truly path-breaking and will certainly lead to changes in the current therapy regime,' Professor Gnant underlines. 'Two injections per year may spare many women severe suffer-

ing.' Today, aromatase inhibitors are the treatment of choice for hormone receptor-positive breast cancer; they suppress the body's natural oestrogen production and thus negatively impact on bone metabolism.

Two further studies showed that adjuvant anti-hormone therapy as well as bisphosphonate therapy could reduce the recurrence rate and mortality of postmenopausal patients with hormone-dependent breast cancer.

The first of these meta-analyses compared the efficacy of adjuvant aromatase inhibitors and tamoxifen. Aromatase inhibitors are administered to suppress the production of oestrogen, which promotes tumour cell growth in hormone-dependent breast cancer, while tamoxifen blocks the oestrogen receptors on the surface of cancer cells which prompt these cells to grow.

Results: post tumour surgery aromatase inhibitor therapy is superior

to tamoxifen therapy. Compared to tamoxifen alone, aromatase inhibitor therapy reduces the risk of recurrence by one third. Moreover, figures indicate that a five-year aromatase inhibitor therapy reduces mortality by 15 percent compared to tamoxifen therapy.

Bisphosphonates are being used to counteract the osteoporosis risk associated with anti-hormone treatment of breast cancer. The second meta-analysis co-conducted at CCC Vienna confirmed the efficacy of bisphosphonates over a period of two to five years post-surgery in postmenopausal breast cancer patients since the occurrence of bone metastases was reduced by 28 percent and breast cancer mortality was reduced by 18 percent. In pre-menopausal breast cancer patients no positive effect could be identified.

'These two meta-analyses will also redefine the standard treatment of breast cancer. In addition, they prove that, with our knowledge and our performance, we are at the forefront of international cancer research,' Professor Gnant happily concludes.

The top performance does not go unrecognised: ABCSG will play a crucial role in the new PALLAS study, which seeks a new strategy for follow-up treatment of female as well as male breast cancer patients. Worldwide around 4,600 breast cancer patients at 500 centres are expected to participate in the study

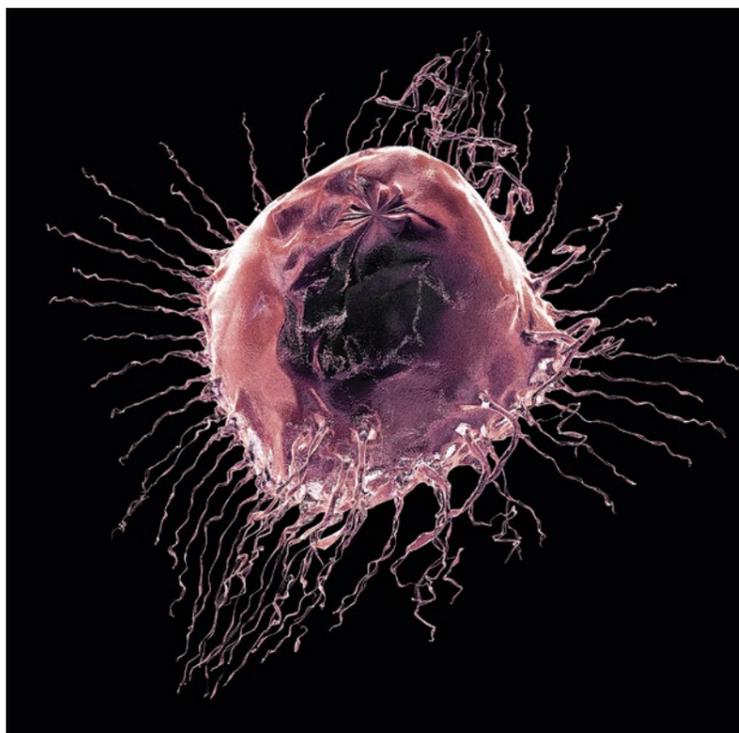


Professor Michael Gnant directs the University Clinic for Surgery at Vienna's Medical University and is Deputy Director of the University's Comprehensive Cancer Centre (CCC). The Vienna-born researcher also presides over ABCSG, the Austrian Breast & Colorectal Cancer Study Group. Additionally, he is visiting professor at the Mayo Clinic in Rochester, USA, and a board member of several national and international professional societies. His research focus is surgical oncology, particularly breast, colorectal and pancreatic. The professor is also interested in antibody immunotherapy, endocrine intervention, tumour dormancy, therapies targeting bones in order to halt tumour micro-metastases and therapies targeting pathways such as mTOR or CDK 4/6 inhibitors.

and ABCSG will coordinate the international – i.e. non-US – part of the study with 2,300 patients. Professor Gnant is understandably pleased: 'For a small country, such as Austria, that's quite remarkable.'

The study looks at patients diagnosed with a stage II or III hormone-dependent breast cancer without HER2 characteristics. After the standard initial therapy (surgery, radiation and chemo therapy) they receive the usual anti-hormone therapy over a period of two years to block metastases or an additional agent: palbociclib.

This substance has been successfully used in the treatment of patients with breast carcinoma metastases (stage IV).



Found: 5 new cancer associated genes and 13 new mutational signatures that influence tumour development

In view: Customised breast cancer care

Report: Mark Nicholls

UK-based researchers believe personalised treatment for breast cancer is within sight after uncovering what they say is the most detailed picture to date of which genetic variations contribute to development of the disease.

With colleagues, study leader Dr Serena Nik-Zainal, at the Wellcome Trust Sanger Institute near Cambridge, identified a number of new genes that, when mutated, drive the development of breast cancer tumours.

In what is the largest-ever study to sequence the whole genomes of breast cancers, the team has uncovered five new genes associated with the disease and 13 new mutational signatures that influence tumour development.

The team's work (published in two papers in *Nature* and *Nature Communications*) also reveals what genetic variations exist in breast cancers and where they occur in the genome.

The research – an international

collaboration which included breast cancer patients from the USA, Europe and Asia – involved analysis of 560 breast cancer genomes – 556 from women and four from men.

Dr Nik-Zainal's team hunted for mutations that encourage cancers to grow and looked for mutational signatures in each patient's tumour.

They found that women who carry mutations in the BRCA1 or BRCA2 gene indicating an increased risk of developing breast and ovarian cancer, had whole cancer genome profiles that were highly distinctive from each other and were also very different to other breast cancers.

She believes that this discovery could be used to classify patients more accurately for treatment. 'In the future, we'd like to be able to profile individual cancer genomes so that we can identify the treatment most likely to be successful for a woman or man diagnosed with breast cancer,' Nik-Zainal added. 'It's a step closer to personalised health-care for cancer.'

Researchers, recognising that unpicking the genetic variations

between cancers is crucial to developing improved therapies, say the results reveal more about the causes of breast tumours and provide evidence that breast cancer genomes are highly individual.

Exactly where mutations occur



Dr Ewan Birney is Director of EMBL-EBI (the European Bioinformatics Institute, which is part of the European Molecular Biology Laboratory). His main research areas include functional genomics, assembly algorithms, statistical methods to analyse genomic information and compression of sequence information.

in breast cancer genomes is also important.

Dr Ewan Birney from the European Bioinformatics Institute collaborated in the research and used computational techniques to analyse the sequence of genetic information held in each of the sample genomes. 'We know genetic changes and their position in the cancer genome influence how a person responds to a cancer therapy,' he said. 'For years we have been trying to figure out if parts of DNA that don't code for anything specific have a role in driving cancer development.'

'This study gave us both the first large-scale view of the rest of the genome, uncovering some new reasons why breast cancer arises, and gave us an unexpected way to characterise the types of mutations that happen in certain breast cancers.'

The Wellcome Trust Sanger Institute is one of the world's leading genome centres, while the European Bioinformatics Institute is part of the European Molecular Biology Laboratory (EMBL) and is a global leader in the storage, analy-



Dr Serena Nik-Zainal MD is a Career Development Fellow (CDF) Group Leader in the Cancer Genome Project at the Sanger Institute in Cambridge and an Honorary Consultant in Clinical Genetics at nearby Addenbrookes Hospital. Having qualified in medicine from the University of Cambridge in 2000, trained as a physician and subsequently specialised in Clinical Genetics, she undertook a PhD at the Wellcome Trust Sanger Institute in 2009 and her research focuses on pursuing biological understanding of the mutational signatures that have been identified in primary human cancers.

sis and dissemination of large biological datasets. It is located on the Wellcome Genome Campus in Hinxton, Cambridge.

Professor Sir Mike Stratton, Director of the Wellcome Trust Sanger Institute, said the study takes scientists 'much closer to a complete description of the changes in DNA in breast cancer and thus to a comprehensive understanding of the causes of the disease and the opportunities for new treatments.'

Detecting bladder tumours

Photodynamic diagnosis locates the smallest tumours

Report: Anja Behringer

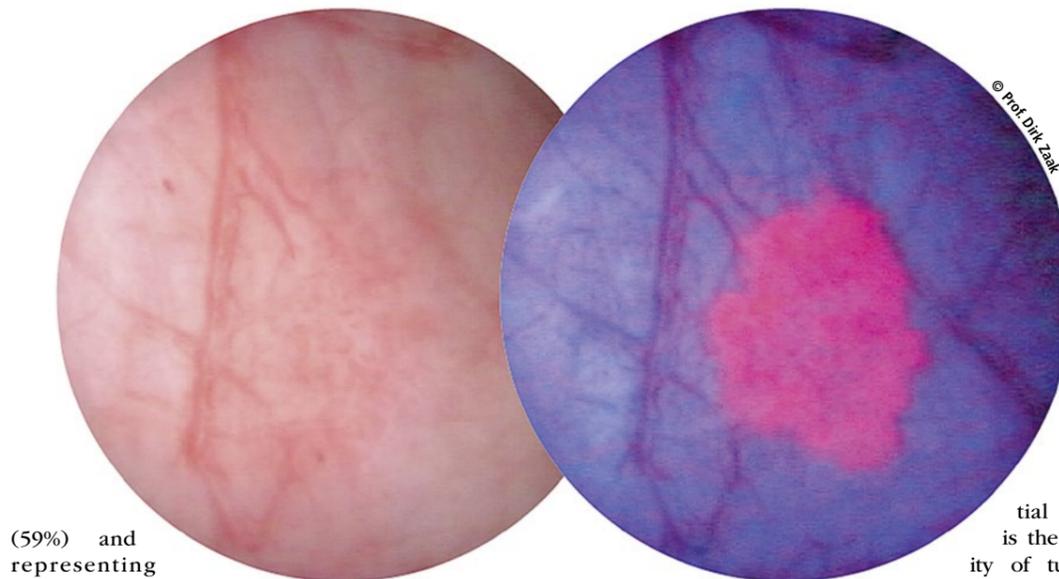
Bladder cancer (BC) is the most common malignancy involving the urinary system and the ninth most common malignancy worldwide. About one in 25 western men (the seventh most common cancer) and one in 80 women (17th position) will be diagnosed some time in life. Transitional cell or urothelial carcinoma is the most common type of BC, accounting for more than 90% of all cases. Urothelial carcinomas are clinically classified as non-muscle-invasive (NMIBC) and muscle-invasive bladder cancer (MIBC).

NMIBC is confined to the bladder mucosa and submucosa and has not infiltrated the muscular wall. 70% of BC cases are NMIBC at diagnosis. NMIBC includes the subtypes Ta (70%), T1 (20%) and CIS (10%).

MIBC has invaded the muscular wall of the bladder and/or spread to nearby organs and/or lymph nodes. 30% of BC cases are MIBC at diagnosis (T2 to T4).

Prevalence and mortality

The worldwide age-standardised incidence rate (ASR) is 10.1 per 100,000 for males and 2.5 per 100,000 for females. The prevalence of bladder cancer is the highest of all urological malignancies. Each year, approximately 110,500 men and 70,000 women are diagnosed with new cases and 38,200 patients in the European Union and 17,000 US patients die from BC. Therefore, the economic impact is important, because it is among the most expensive cancers to manage. The total cost has recently been estimated to be €4.9 billion in 2012, with healthcare accounting for €2.9 billion



(59%) and representing 5% of the total

cancer-related healthcare costs across the EU (Leal et al., Eur Urol. 2015). The management of early stage bladder cancer therefore represents a potential target for major healthcare savings. The risk of developing bladder cancer increases with age and the median age at diagnosis is 70 years. Women are diagnosed less often than men, but tend to have more advanced disease at diagnosis because bladder cancer is less often suspected. The main symptom for NMIBC is painless haematuria. In patients with CIS, haematuria may be accompanied by irritative voiding symptoms such as urinary frequency, urgency, and dysuria. Physical examination does not reveal NMIBC.

The diagnosis of bladder cancer is made by cystoscopic examination of the bladder including biopsy (an invasive examination method) and histological evaluation of the resect-

The photoactive fluorescent substance Hexvix makes even the smallest tumours clearly visible in pink.

ed tissue. Urine cytology is a non-invasive method for detecting bladder cancer by identifying abnormal urothelial cells in the voided urine or bladder washes. Although urine cytology remains the gold standard test, many new urinary biomarkers have been identified in recent years. Imaging examinations include conventional intravenous or computed tomography urography (X-ray examination with contrast agent) and ultrasound (can show tissue changes, tumours, hydronephrosis).

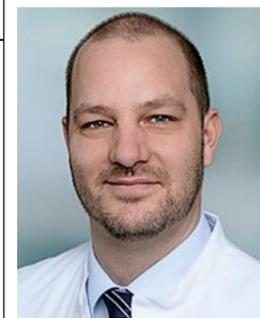
A transurethral resection (TURB) is the standard treatment for bladder tumours. The aim of the initial TURB is to remove all visible tumours and obtain tissue for accurate histological diagnosis. An important factor that influences the outcome of the ini-

tial TURB is the visibility of tumours.

Hexaminolevulinat hydrochloride (HAL)-guided blue-light cystoscopy improves visualisation of tumours during TURB, helps the urologist to identify tumour margins and confirms complete clearance of lesions. The guidelines recommend the use of fluorescence-guided resection as being more sensitive than conventional white-light cystoscopy to detect tumours.

Optimised photodynamic diagnosis

At the 31st Annual Congress of the European Association of Urology Professor Thorsten Bach of the Asklepios Hospital in Hamburg reported on his experiences with PDD (photodynamic diagnosis)-assisted cystoscopy using Hexvix (HAL). 'The malicious thing with bladder cancer is the high risk of recurrences. Therefore, it's so important to remove even the smallest tumours without lesions, as in



Professor Thorsten Bach heads the Department of Urology at the Asklepios Hospital, Harburg, in Hamburg. In 2008, he was a Fellow of the Endourological Society, specialising in endourology and minimally invasive urology. Laser enucleation of the prostate, among others, is another specialty, utilising a Thulium laser – he has performed and published the fundamental research on this laser tool, which have gained him national and international awards. He is a member of the German Working Group on Urolithiasis as well as the EAU Section of Urolithiasis (EULIS) and EAU Section of Urotechnology (ESUT), and also a member of the EAU Guideline panel on Male LUTS, plus a Chairman for the EAU Patient Information Project (<http://patients.uroweb.org/>).

between a third to half of all cases, new ones occur after six weeks.'

To detect them more reliably and at an earlier stage than is possible with the conventional white light cystoscopy the photoactive, fluorescent substance Hexvix colours existing tumours pink, against a blue background. 'This allows the discovery of 7% more tumours as proven by a study from Denmark and real-life experience from the UK last year.' When EH asked about the costs involved, Bach explained that Hexvix has been covered by the DRG system since 2014. 'The additional costs pay off through reduced costs spent on intervention, as proven by the Danish study.' The improved pharmacokinetic characteristics of the only currently licensed medication for PDD have been described in the new S3 guideline on bladder cancer, published in May. ■

Spanish Society of Radiotherapy and Oncology (SEOR) pushes for guidelines

Demand to regulate oncologic hyperthermia

Unlike the USA, Italy, Germany or the Netherlands, Spain does not include hyperthermia in its national health catalogue. Worse, many non-medical centres are increasingly offering hyperthermia as an alternative treatment, a situation that infuriates Spanish oncologic radiotherapists.

The Spanish Society of Radiotherapy and Oncology (SEOR), representing over 1,000 of radiotherapists, is pushing for guidelines to regulate the use of oncologic hyperthermia and include it in cancer radiation therapy routine.

'Having a regulatory framework is the only way we can avoid proliferation of such centres. Oncologic hyperthermia must be indicated, controlled and supervised by oncologic radiation therapists; they are the only people who can prescribe and apply it. Hyperthermia can be an asset when combined with other conventional treatments, such as surgery, radiotherapy and chemotherapy,' explained Jorge Contreras, director of Magna Clinic Marbella

and coordinator of the SEOR working group on hyperthermia.

Hyperthermia is relatively easy to produce and administer; basic equipment used in physiotherapy or cosmetics can produce hyperthermia, which is why many non-medical centres can offer hyperthermia as an alternative medicine.

However, the only guarantee the treatment will work is when oncologists control the whole process,

Contreras said. 'When hyperthermia is applied without knowing the full treatment combination, therapy may not be successful. Then there's a risk of strengthening secondary effects induced by treatment instead of improving it.'

The goal of hyperthermia is to boost treatment effect and immune system response. It can also improve blood flow and muscle relaxation, and alleviate symptoms.

International studies are starting to show that hyperthermia can improve treatment of breast cancer, soft tissue sarcoma, colorec-

tal and pancreas cancer, and brain and head and neck tumours, such as larynx and oral cavity tumours. Researchers are also working on validating hyperthermia in other applications – prostate cancer, central nervous system tumours, e.g. multiform glioblastoma, lung cancer.

Contreras plans to use these results to foment guidelines. But he insisted on the value of conducting such studies in Spain as well. He deplors this fact: 'The lack of nationwide-scale studies in our country does not help.'

The technique was only introduced last year in Spain, but only a few hospitals so far offer hyperthermia and have the right personnel.

Other challenges of radiation cancer therapy, a subspecialty recognised over 40 years ago in Spain, include better equipment and personnel distribution countrywide, and wider access to technologies, such as proton therapy. Only tertiary centres in Madrid, Barcelona and Valencia have all the latest available technology. Additionally, projects to include proton therapy in the nation's health service catalogue are underway. ■



Jorge Contreras is Radiation Oncologist and Head of Training at Carlos Haya Hospital in Malaga. He also sits on the tumour board and is president of the head and neck tumour board. He is part of many scientific societies including the Spanish Association of Radiation Oncology, the European Society for Therapeutic Radiology and Oncology (ESTRO), and the American Society for Therapeutic Radiology and Oncology (ASTRO). In addition, he coordinates the group for the Development of Hyperthermia in Oncology of the Spanish Society of Radiation Oncology.

Proton therapy enables tumour treatment more locally and more radiation dose while reducing secondary effects. All especially useful for brain tumours, medullar cancer and tumours in delicate areas. However, most tumours are not that localised, Contreras pointed out. '95% of tumours can be treated with currently available technology.' ■

Creating a data powerhouse

In her **Keynote address** at the forthcoming Digital Pathology Congress (London, 1-2 December) Dr Fiona Carragher, the Deputy Chief Scientific Officer for NHS England will discuss 'Personalised medicine - The next dimension for digital pathology', in the context of the NHS England Personalised Medicine strategy, and how digitisation, combination and analysis of diagnostics is central to personalised care. Ahead of the congress, she shared her views exclusively with Mark Nicholls of European Hospital.

'The combination, correlation and analysis of information are the cornerstone of personalised medicine,' Dr Carragher pointed out. 'It is the ability to digitise results from patient samples that has been one of the key enabling technologies that make personalised medicine possible now. Through digitising information in this whole-scale way we can apply new analytical techniques, such as machine learning and cluster analysis that open up possibilities for new diagnoses and characterisation that weren't possible with the previous approaches.'

Is NHS England close to embracing personalised medicine through these means?

'In the NHS we already have the foundations in place to bring the science and data together through our integrated informatics and genetic laboratory infrastructure. The NHS has spearheaded this new

way of working by establishing 13 NHS Genomic Medicine Centres. These are pioneering and multidisciplinary network structures that require input across many clinical specialities. They are a step change in the processing of information, as they capture data from multiple systems and bring this together to analyse against common datasets and standards. Thanks to this infrastructure, by 2020 we aim to be offering whole genome sequencing for specific conditions; improved diagnosis of rare conditions and a better understanding of cancer; and comprehensive linked diagnostics data coupled with effective informatics analysis to give a full picture to patients.'

The next stage

'We are continuing to develop the building blocks currently in place, with a focus on improving connectivity; educating, informing and supporting commissioners; quality and accreditation, and developing informatics and analysis capacity. More specifically, we are developing our specialist genetic and molecular pathology laboratories; investing in the data and informatics infrastructure for the NHS Genomic Medicine Centres; and working with Health Education England to develop the workforce capability and expertise to deliver genomic and personalised medicine.'

'By 2025 we hope to achieve a new taxonomy of medicine based

on underlying cause and personal response; an integrated clinical service taking a "whole body approach"; and tailored, optimised and more effective therapies for better outcomes.'

How much investment is needed?

'There are many external factors that will influence the success of this vision and it's vital that we develop a shared ambition and commitment to deliver this with partners across the system and beyond. One key investment is in building partnerships between the NHS, academia, industry and patient groups - as maximum patient benefit will come where all these groups work together.'

'The future of digital pathology can only be delivered through enduring collaborative relationships and networks that ensure national consistency whilst delivering local responsiveness. To achieve this we need to invest in meeting the training, education and workforce planning challenges; facilitate the uptake and adoption of new scientific advances and technology; understand funding flows; develop commissioning information and education tools with commissioners; develop new models of care, and ensure quality and assurance.'

How will its worth and success be quantified?

'High quality diagnostic services are crucial to both patient outcomes

and in determining success of other targets and measures for the whole system. This is because they are at the front line of screening and assessment to diagnose disease and determine severity, functional impact and response to therapeutic intervention. As they form such an integral part of clinical decision making, digital pathology is a key driver in successful and sustainable delivery of A&E targets, Referral to Treatment Times for elective and out-patient care, reduction in hospital admissions and in length of stay.'

The NHS Personalised Medicine Strategy

'Personalised medicine is a move away from a "one-size-fits-all" approach to the treatment and care of patients with a particular condition, to one which uses new approaches to better manage patients' health and target therapies. The NHS Personalised Medicine Strategy is changing the way medicine will be delivered to follow a targeted treatment approach enabled by integrated informatics. It turns on its head the traditional approach built around clinical teams specialising in a particular organ system, who work back from a patient's symptoms to arrive at a diagnosis.'

'Personalised medicine recognises that complex diseases should no longer be considered as a single entity. As we integrate and analyse genomic and other data, we can find common factors and causes of variation, resulting in the discovery of new pathways of disease, which changes how diseases are thought of and treated. It enables us to recognise that the same underlying change in our DNA or genome can lead to problems in very different parts of the body, which would not have been previously identified with a more traditional care approach.'

Central to personalised care: dig-



Dr Fiona Carragher is the Deputy Chief Scientific Officer for England, supporting the head of the profession for the 50,000-strong healthcare science workforce in the National Health Service (NHS) and associated bodies. This covers more than 50 separate scientific specialities. With a clinical background, and as a Fellow of the Royal College of Pathologists, she has a broad portfolio of policy responsibilities across NHS England and the wider NHS and provides professional leadership and expert clinical advice and particularly for pathology within NHS England. A significant part of her role involves working across government, with partners in the Department of Health, the NHS, Public Health England, Health Education England, and others to help inform policy, influence legislation, deliver strategic change and introduce new ways of working.

Integration, combination and analysis

'An integrated characterisation of individuals, based on the diagnostic and clinical data the NHS generates, is central to personalised medicine. We have more data about people, their habits and their health than we've ever had. To maximise the true value of the available information, we need to bring together genomic, clinical and diagnostic, medicines, and lifestyle data. It's the integration and analysis of this information that forms the power-

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In the 21 years since its launch in Germany, Kugel medical has become a leading manufacturer of histopathology equipment on a global level, with a presence in laboratories, forensic centres, universities, anatomical institutes, pharmacy firms and veterinary pathologies. The products include almost everything used in a modern laboratory. 'Our specialties are the integrated exhaust units for dissection and autopsy tables,' explains CEO Robert Karl. 'We also offer a complete range of stainless steel furniture, morgue refrigeration units and transport and storage equipment, which are distinguished by their ease of use, installation and maintenance, high reliability and long service life.'

Recently, Robert Karl has been consistently asked not only to provide equipment, but also to perform entire laboratory planning. 'It makes no difference whether you're looking for a partner for sophisticated furnishing of an entire building complex or a partial fit out.'

'We are your point of contact for all questions concerning design, development, planning and implementing,' adds Claudia Karl, CFO at Kugel medical. In such cases, Robert Karl and team work closely with

architects and engineers to arrive at a perfect arrangement of workspaces and compliance with government regulations and limits for alcohol, formalin and xylol concentration. Based on extensive discussions with their international customers, the company designs a tailored concept

that suits their customers' needs.

Modern 3-D drawings enable customers to gain a realistic impression of their future laboratory. 'On the technical side, exhaust and ventilation technology has never been more important than now, especially energy recovery and filtration of

pollutants play a main role,' Robert Karl points out.

Kugel now exports to 72 countries, assisted by about 130 business partners. Thus the firm's advanced solutions are internationally - in the renowned Medical Faculty of the University of Melbourne, Australia;

Our Lady of Maryknoll Hospital in Hong Kong; Hospital No. 4 in Olympic City, Sochi, Russia; the Charité in Berlin, one of Europe's biggest university hospitals, and more.

The firm reports that it has worked with some of its business partners for over a decade. 'Something we



Designs for specific work spaces and their devices



house for personalised medicine.'

What could other NHS services learn from digital pathology?

'The key lesson is in demonstrating how existing approaches can be transformed by using new digital technologies. Digital pathology and diagnostics are leading the way in the integration of services by establishing new models of care that are delivered locally and organised in a way that improves care in patients with complex conditions. Furthermore, digital pathology is driving research and innovation within the NHS, raising the game on healthcare technologies, undertaking a radical upgrade in prevention and public health and giving greater focus to primary care and the control patients have over their care.'

What will benefit hospitals/clinicians from personalised digital pathology?

'With pathology having always been a key part of the diagnostic repertoire, our aim is to develop state-of-the-art diagnostic services in the NHS, underpinned by an effective commissioning system to deliver safe, effective and timely care for patients. To achieve this, hospitals and clinicians will benefit from working together to form multi-specialty community providers to deliver a range of diagnostic services with a different workforce skill mix. This will potentially offer greater value for money and a reduction in waiting times as they are delivered at the point of care.'

'Hospitals and clinicians will also benefit from the 'vertical integration' of hospital diagnostic services, with primary care diagnostic services organised in a continuum linked by technology. Furthermore, we are establishing hubs of diagnostic excellence to drive quality, efficiency, innovation and research.'

Patient benefits

'There are four key benefits for patients: Firstly, personalised medicine drives prediction and prevention of disease. We'll be able to identify the people most at risk of disease even before the onset of their symptoms. Earlier detection will open up the prospect of new treatment options and support people to make informed lifestyle choices.'

'Secondly, personalised medicine enables more precise diagnoses. Knowledge of each individual's

complex molecular and cellular processes, informed by other clinical and diagnostic information, will enable us to fully understand the abnormal function and determine the true cause of the symptoms.'

'Thirdly, personalised medicine will enable targeted and personalised interventions by offering the opportunity to move away from "trial-and-error" prescribing to optimal therapy first time round.'

'Finally, personalised medicine will enable a more participatory role for patients. The ability for

a clinician to discuss with their patients information about individual genomic characteristics, lifestyle and environmental factors, and interpret personal data from wearable technology will drive a new type of conversation.'

The broader implications

'By delivering the right decisions and interventions sooner, personalisation will not only deliver better outcomes for patients but ensure the NHS makes better use of resources – particularly the £15 billion annual

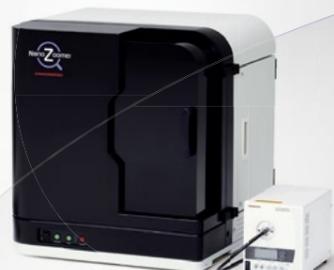
drugs budget and the £8 billion annual diagnostics budget. Through personalised medicine we can also strengthen our ability to design appropriate health and care for our local populations through a more sophisticated understanding of the impact of age, gender and ethnicity, or lifestyle factors that influence the onset of disease. This will enable us to be far smarter in the way that we manage and leverage the limited resources we have.'

Solutions for Digital Pathology

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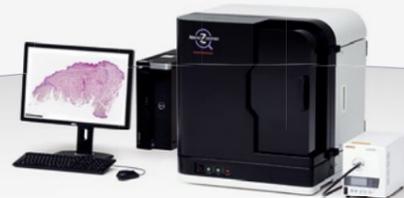


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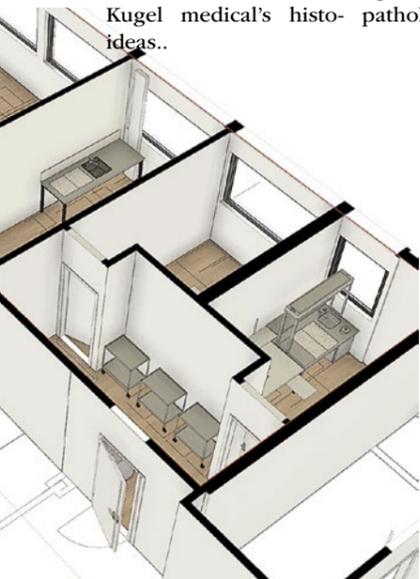
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- High-speed and sensitivity in fluorescence
- Best image quality both in brightfield and fluorescence
- Double-size slides scan
- Ideal for all research and pathology laboratories

needs

are very proud of", says Claudia Karl. At the moment, the entrepreneurial couple is aiming for a foothold in Latin America. 'The upcoming MEDICA 2016,' she believes, 'is the perfect contact platform for us to meet new business partners from abroad and from overseas in particular.'

Meet them at Medica 2016 in Düsseldorf, this November. Go to Hall 3, booth E92 to experience Kugel medical's histopathology ideas..



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Digital pathology advances personalised medicine

Successful digital pathology

Denmark has been highlighted as a world-leader in creating a hugely successful national digital pathology system, Mark Nicholls reports

Advanced computer software underpins a service - coupled with a countrywide database, which enables Denmark's pathologists to optimise the assessment of patients' specimens.

In turn, the digitisation of the system in recent years has led to significant improvements in pathology services, delivering greater efficiency and advances in patient safety.

Professor Ben Vainer, who will highlight the progress his country has made in this field at the Digital

Department of Pathology at Rigshospitalet, at the University of Copenhagen, will focus on the Danish civil registry database and other national databases connected to this, and the use of the same laboratory information system (LIS) in all pathology departments in the entire country, with access to the national pathology database of all pathology reports in Denmark since at least 1998.

He believes this gives Danish pathologists unique opportunities



Grossing. Each person has his/her own screen, which shows specimen details and other software can be opened, for example a surgery report or laboratory tests. Two people are always present, one for the grossing and for packaging etc. The latter ensures patient identification and use of the correct capsules/blocks



Ben Vainer is Professor of Pathology at the University of Copenhagen and consultant pathologist at Department of Pathology, Rigshospitalet, the University of Copenhagen's main teaching hospital. His primary area of interest is digitisation of pathology in terms of education, research and diagnosing.

Block cutting. The screens to the technicians' right are used to ensure patient identification. Each block and glass slide are to be 'beeped'; if the block and glass are not from the same specimen the system will make a sound and show a big red X; then it becomes impossible to proceed unless the technician corrects the mistake



Whole slide image workstation: right screen for microscopy, middle for LIS, left for other software, e.g. radiology, patient record or laboratory workup

Pathology Congress (London, 1-2 December), believes other nations can learn from the Danish experience.

Ahead of his presentation, 'How digitisation can improve pathology service - The Danish experience,' he told European Hospital: 'In large pathology labs, the high number of specimens is often a hindrance to efficient handling and ensuring patient safety without time-consuming steps, but those steps can be turned digital, releasing valuable staff resources.'

'Most important, though, is that digitisation opens up opportunities for the implementation of the new imaging techniques, which are necessary to provide each patient with the correct assessment of diagnosis and biomarker expression profile.'

Vainer, a consultant in the

to interact with each other and to study diseases from an epidemiological point-of-view.

His talk will focus on the advantages of these national initiatives, giving an overview of computerisation and digitisation in routine laboratory operations, from the clinician's ordering of a service via tissue sectioning and staining, to speech recognition and report presentation to the ordering clinician and to research-related national cancer databases.

Vainer will also discuss the important links between LIS and patient medical records in hospitals and in private practice (e.g. general practitioners), and how computerisation of the entire laboratory flow, from ordering of the pathology service to presentation of the specimen to the ordering physician, has helped

ensure patient safety and eliminate time-consuming manual steps.

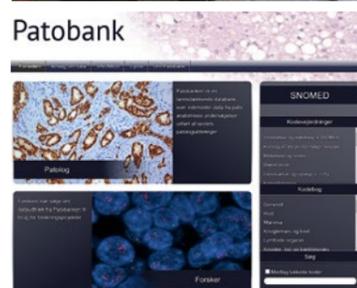
'Pathology departments in Denmark have, through close collaboration, been able to build a national pathology system, where each individual pathology department serves as a sort of "branch office",' he added.

'All steps of the specimens are followed through the pathology department, which gives a good global view of the departmental activities and the possibility to trace individual specimens. For the managers, this also provides good measures of operational objectives.'

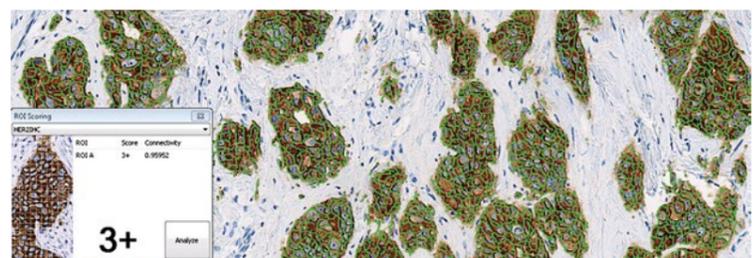
The "users" - the ordering physicians - are provided with a clear overview of their patients' specimens during the assessment process, and the patients have full access to reports on their own tissue,' he added.

Digitisation of the laboratory processes and the link to the pathology LIS and the national pathology database opens up the opportunity for image automation, including digital image analysis and transfer of whole slide images in cases where a second opinion is needed, without compromising patient safety or the international data acts.

Patients in Denmark are also seeing clear benefits from digital pathology with a significant reduction lost specimens. 'The risk of specimen mix-ups are minimised, and application of national pathology databases linked to national person-identification databases ensures that the pathologist always has access to previous tests performed on the patient,' Vainer point-



Patobank is the national pathology database, which includes all pathology reports since at least 1998 (and diagnosis back to around 1988). This is the homepage, also including the detailed SNOMED coding database (in Denmark this has more than 7,000 entries).



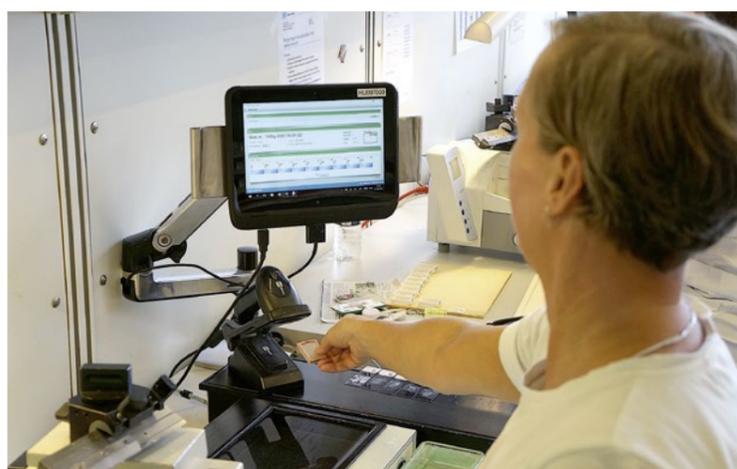
ed out. 'This increases the quality of the pathology assessment and hence the final diagnosis.'

The process within Denmark is constantly evolving with the intro-

Digital image analysis of HER2 in a breast cancer case. The software provides a semi-quantitative score according to international guidelines (0,1+,2+ or 3+)



Registration of incoming specimens (in the plastic bag in front of the technician). Tubes are suction (to avoid formalin fumes)



The system in action; the technician is scanning the barcode, which is on the side of the tissue block

duction of the new digitisation procedures, such as automated image analysis, and substitution of conventional light microscopies with whole slide images.

'Automated image analysis,' he said, 'will further increase the pathology assessment quality by eliminating subjective readings of biomarker expression, for example, in addition to eliminating the risk of patient case mix-up.'

* Ben Vainer, Professor of Pathology at Copenhagen University, will discuss developments on 2 December during the Digital Pathology Conference, to be held at London's Heathrow Marriott Hotel.

Increase confidence in the operating theatre

Adapting to image guided surgery

In more than 21% of complex anatomical osteosynthesis procedures, an intraoperative improvement of the implant position or a revision of reduction has to be performed (Recum von, J. et al., Unfallchirurg 2012, 115:196-201, Die intraoperative 3D-C-Bogen-Anwendung. State of the art). Image-guided surgery is gaining relevance as a method to increase confidence in these complex procedures.

The goal is to enable clinicians to deliver high-quality care and manage less-invasive approaches to shorten hospital stays, which potentially improve patient outcomes. By utilising preferred, navigation-ready instruments from different implant companies, automatic registration of images for navigation and intraoper-

ative 3-D control scans allow quick progress checks and documentation at all times. This, in turn, ensures efficient clinical workflows, contributing to increased accuracy and reduced X-ray exposure (Richter et al., Cervical pedicle screws: conventional versus computer-assisted placement of cannulated screws. Spine (PhilaPa 1976). 2005 Oct 15;30(20):2280-7. And, Gebhard et al., Does computer assisted spine surgery reduce intraoperative radiation doses? Spine (PhilaPa1976). 2006 Aug 1;31(17).

For these demanding procedures in areas such as the cervical and upper thoracic spine, as well as for pelvic or minimally invasive surgeries, Ziehm Imaging partnered with leading surgical navigation provid-

ers to develop an interface that combines navigation systems and intraoperative 3-D imaging with the Ziehm Vision RFD 3D mobile C-arm.

The Ziehm NaviPort navigation interface connects the C-arm seamlessly with the navigation system. A high-resolution 3-D dataset can be transferred automatically; real-time visualisation of the surgical instrument position can then be performed on the acquired dataset. This allows more accuracy during orthopaedics, trauma, and spinal procedures compared to conventional surgical techniques.

With the combination of advanced intraoperative 3-D imaging and navigated surgery, these complex procedures for accurate screw and implant positioning can be han-



dled with greater confidence thanks to visual guidance requiring less fluoroscopic control. With image-guided surgery and intraoperative control scans, post-operative CT scans become obsolete. 'Moreover, the ability to perform intraoperative

control scans enables us to significantly reduce the need for postoperative CT scans,' says Professor Christoph Josten, Orthopaedics, Trauma, and Reconstructive Surgeon at Leipzig University Hospital

Seeking the gateway towards deeper computer intelligence

Cognition-guided surgery

Surgery will change – with all the challenges that developments such as Big Data create there are no two ways about it. However, how deep those changes run remains to be seen. In a rather young field of research, scientists look at the ways all components used during surgery can be interlinked. Professor Beat Müller, co-initiator of the project 'Cognition-Guided Surgery', explains results achieved so far and coming challenges

Report: Marcel Rasch

Cognition-guided surgery aims to enable surgeons to make knowledge-based computer-aided decisions during surgery – with the help of computers. This requires the creation of a database that is filled with factual and practical knowledge that a machine can process and use.

The underlying idea is for a surgeon to be able to call up suitable actions when planning or performing an intervention. 'You can compare it to a cognitive vehicle. While we are in the car driving along the road we often don't notice that there are technologies in the background that control traction or chassis or whatever. When problems occur, a warning is displayed. As an advanced development, the cognitive car is autonomous, entirely disconnected from the human driver,' Professor Beat Müller explains.

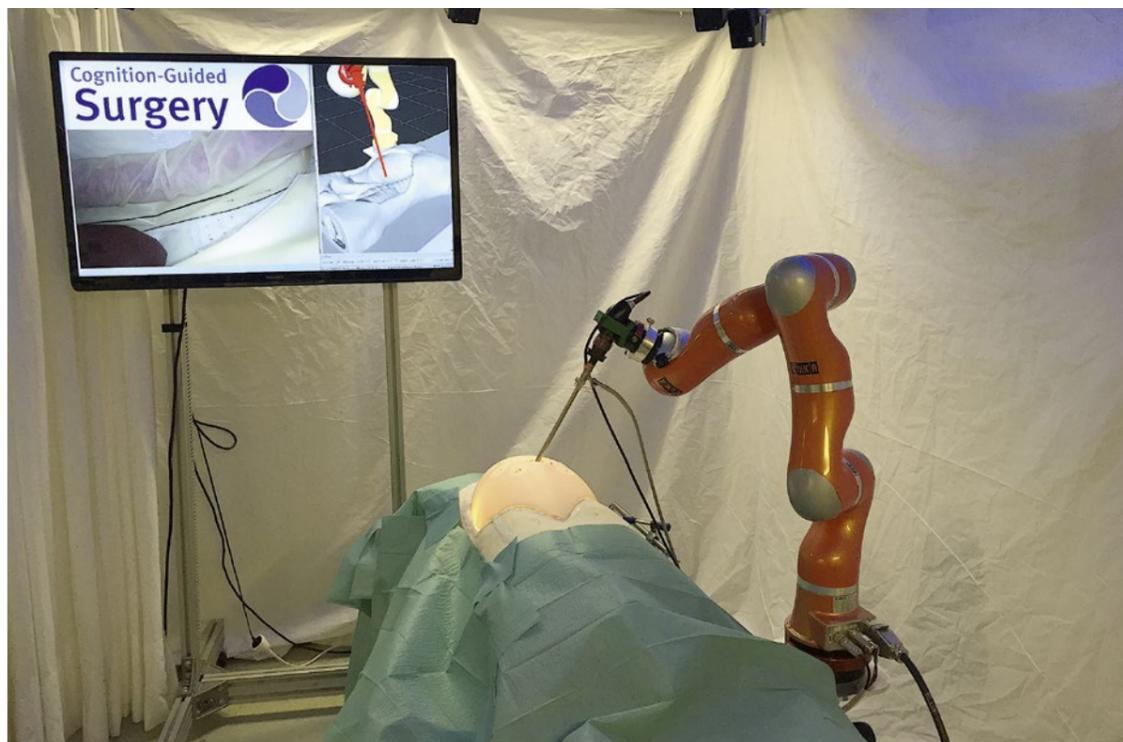
The human brain can process or access a maximum of about seven

pieces of information at a time. However, large amounts of data are not a problem for a computer. The challenge for the machine is not data volume but data interpretation. 'In surgery we are dealing with massive data volumes. Every day, new knowledge is published in thousands of books and articles, new insights are culled from diagnostics, which is an increasingly complex discipline. A few decades ago X-ray images were all we had; today we are looking at CT and endoscopy images, at lab and histology parameters previously unknown.

'To collect these data and channel them into a sound decision – that's the complex art of medicine. Unfortunately humans do make poor decisions every once in a while. Thus cognition-guided surgery wants to create a system that helps to make good decisions.'

Initial results

That's a long way to go. It won't



suffice for scientists to access Big Data and to design analytical tools; they must consider a very special factor, as Müller points out: 'The ability to learn is a crucial feature of the machine. The computer must be able to process not only factual knowledge, or book knowledge, but also practical knowledge gathered over time in the course of our everyday work. All these types of knowledge are input for the knowledge base. What we are aiming at is a system that does not suggest certain procedures anymore, because of the negative outcomes this procedure yielded in the past. Instead the system suggests only procedures with a higher probability of success.'

Such a system might indeed work, as was demonstrated by an initiative funded by the German Research Fund (DFG) between 2012 and 2016. 'In the special research area Cognition-Guided Surgery, teams from a consortium of researchers, including the German Cancer

Research Centre and the Karlsruhe Institute of Technology, looked at several key aspects of this idea,' Müller reports. In the course of the project an adaptive autonomous camera-guidance robot was developed. 'When the computer correctly guided the camera during an intervention, this experience was stored as "positive".

'But when the camera-guidance robot was corrected, it stored the correction,' he explains. Thus the system learns the correct camera positions step by step.

The road ahead

However, many challenges lie ahead. 'Don't forget – we are at the very beginning of our research,' says Müller, dampening unrealistic expectations. 'On the one hand we have to make the required data available in a machine-compatible way. When, as trained physicians, we look at an X-ray image and can read it – we understand what we

are seeing. The more X-ray images we read, the more we learn. The computer must also go through this phase of gathering experience and knowledge.' On the other hand, Müller explains, 'a computer can easily do statistical analyses, but semantic assessments are a major obstacle. We are talking about model-based or pattern-based action. It's not only about gathering data but about the way these data are perceived and evaluated.'

A third difficulty is system validation. 'The computer has to show that its suggestions, which are based on the learning process, are indeed better. Human beings learn from success and failure. Machine learning happens in smaller increments. If an error made by the system is not corrected, the system will store it as "positive", no matter whether there might have been specific reasons for not correcting the error in this particular case. In short: We must ensure the system not only gath-

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Successful brain functions transfer

Pioneering cancer surgery

Brain cancer treatment is taking a major step ahead as Spanish surgeons pioneer a new technique that spares language and motion functions. This splendid development might even one day result in epilepsy surgery. Mélisande Rouger reports

A significant number of brain tumour cases have long been considered inoperable due to the extent of the lesion into 'eloquent' areas, meaning those that control vital functions such as language and motion.

A team of Madrid-based surgeons are now injecting new impetus to brain tumour therapy, by enabling cancerous tissue resection without damaging brain function.

During our *European Hospital* interview, Dr Juan Barcia, study coordinator and head of the neurosurgery department at San Carlos University, in Madrid, explained how the idea of transferring function first arose. 'Back in 2007 one of our patients presented an aggressive tumour that we couldn't fully extir-

pate. Typically, these patients died, because we couldn't touch these brain areas. So we thought of moving functions to other, healthy areas nearby, by stimulating them,' Barcia explained, following the recent publication of his results in the *Journal of Neurosurgery*. In his first attempt to migrate function, Barcia used transcranial magnetic resonance – and failed because stimulation time was too short. Inspired by equipment used in epilepsy treatment, he then decided to place a grid of electrodes to continuously stimulate and thus induce plastic reorganisation.

First, he operated on his awake patient and removed the part of the tumour devoid of function. Then, he placed the grid directly over the



Juan Barcia, Head of Neurosurgery at Madrid's San Carlos University

areas affecting function. Through the grid, he provided continuous and increasingly intense cortical electrical stimulation to the functional areas to artificially cancel function and enable the brain to transfer function to nearby areas.

The intervention was coupled with

appropriate behavioural training – also called pre-habilitation – in which the patient repeats the function that is being transferred over and over. Three weeks later, when the maximal stimulation voltage in all active contacts induced no functional deficit, he successfully resected the tumour more extensively.

Between 2009 and 2014, Barcia successfully operated on four more patients with WHO Grade II and III gliomas affecting the eloquent areas.

He used intraoperative mapping and functional MRI to demonstrate plastic reorganisation. 'Most previously demonstrated eloquent areas within the tumour were silent, while there was new functional activation of brain areas in the same region or toward the contralateral hemisphere,' Barcia explained.

The role of behavioural training is fundamental. 'Pre-habilitation with continuous cortical electrical stimu-

lation and appropriate behavioural training prior to surgery accelerate plastic changes,' he added. 'This can help to maximise tumour resection and, thus, improve survival while maintaining function.'

So far the technique has only been used in gliomas, but Barcia believes it could also work in other tumours and further applications, such as epilepsy surgery.

The project attracted very positive response from the field after its presentation during the annual meeting of the American Society of Neurological Surgeons in Chicago and the European Association of Neurosurgical Societies last year in Madrid. 'We've been approached by different groups to design a European study,' he said.

Patients also contacted Barcia and his team after their work was featured in one of Spain's most popular radio shows last May. ■



Leading senior physician **Professor Beat Müller MD**, Head of Section for Minimally Invasive and Bariatric Surgery at the Department for General, Visceral and Transplantation Surgery at Heidelberg University Hospital, also researches computer-based surgery. He has been lead investigator in several interdisciplinary and multi-partner research projects such as 'Intelligent Surgery' and 'Cognition-Guided Surgery' (both underpinned by the German Research Fund (DFG) until 2014 and 2016 respectively). Beat Müller is also a key participant in InnOPlan (Innovative, Data-driven Efficiency of Surgery-related Process Landscapes), a project funded in the framework of the technology programme 'Smart Data – Innovations from data' by the German Federal Ministry for Economic Affairs and Energy, and the EU-funded project COMBIOSCOPY (Computational biophotonics in endoscopic cancer diagnosis and therapy).

ers knowledge but that it indeed improves. Poor approaches to learning might very well lead to poor therapy suggestions. And the worst-case scenario is that we don't even realise that the surgeon performs worse with computer aid than without it,' Müller warns.

Despite these caveats, the vision is alive. 'There is enormous potential to make surgery safer and more efficient,' Müller believes. However, today there are only a few isolated solutions and there are not enough research partners for large interdisciplinary research projects. 'However, if we look at cognitive vehicles again, there are market-ready solutions claimed to be safer than human drivers. This is what I'd like to achieve for surgery.'

Details:
<http://www.cognitionguidedurgery.de>
http://rob.ipr.kit.edu/837_1586.php

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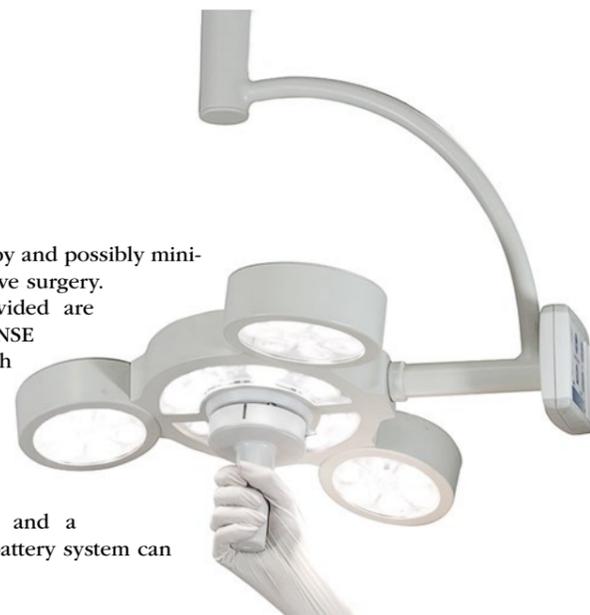
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'To maintain high level care, you should only have a low number of transplant centres'

Top anaesthesiologist stresses automation limits

Mechanical ventilation and sub-specialisation are key aspects of modern anaesthesia and critical care practice according to Dr Javier Garcia Fernandez, Head of Critical Care and Anaesthesiology at University Hospital Puerto de Hierro in Madrid. Interview: Mélanie Rouger



Among the first three European hospitals to perform lung transplants, Puerto de Hierro performs fifty of these operations annually, so far treating around seven hundred patients



In late 1996, Javier Garcia Fernandez gained his PhD in Medicine and Surgery (CUM Laude) at Complutense University of Madrid. After specialising in paediatric anaesthesia and critical care in La Paz Children's Hospital for 14 years, from 2011 he has chaired the Anaesthesia, Critical Care and Pain Department at Puerto de Hierro University Hospital in Madrid. Today he is Professor of Anaesthesia and Critical Care in the Surgery Department at Madrid's Autonomous University. He is also president of the research and ethics committee (REC) of Puerto de Hierro Hospital and associate editor of several international anaesthesiology, resuscitation and ventilation journals.

Prior to his current role at Madrid's University Hospital Puerto de Hierro, Dr Javier Garcia Fernandez practiced as a paediatric anaesthesiologist. Asked what differences need consideration in anaesthesiology and ventilation of children compared to grown-ups, he explained: 'Paediatric anaesthesia is totally different from the rest of anaesthesia. Evidence shows that specialising even only one year in paediatric anaesthesia reduces mortality.'

'The patient's age is crucial. If he or she is six years or older, differences will not be that important and general anaesthesiologists can handle the patient. But little children and neonates require training at a dedicated paediatric hospital.'

'You need specific skills to place something as simple as an intravenous line or connect an electrode on a neonate's thorax.'

'Ventilation is also completely different in children and they respond differently to anaesthetics. It's easier to predict reactions in adults. Fentanyl is a commonly used drug in all patients, but you cannot intro-

duce it as rapidly in a neonate as you would in an adult.'

'And, you can absolutely not miss regarding dose; you need to calculate it perfectly according to the size and weight of the patient.'

'Accuracy and precision are mandatory in children. There is no margin of error.'

Congenital cardiovascular disease surgery and transplants



are the most common settings for paediatric anaesthesia. Are there enough anaesthetists in Spain to properly care for these patients?

'All studies show that paediatric anaesthesia in these settings should only be done at paediatric hospitals. There should not be more than three or four hospitals offering paediatric transplants in the same country. These procedures are complex and you need to treat enough patients to obtain good results.'

'La Paz in Madrid was one of the first hospitals to offer paediatric transplants. But, in Spain, healthcare is divided in 17 different areas and all are trying to get their own paediatric hospital.'

The British model is excellent in my opinion for transplants and running the extracorporeal membrane oxygenation (ECMO) programme. Six centres are authorised to perform transplants and run ECMO. They are evaluated every year and only the most efficient can continue their activities.'

'Nevertheless there should be enough paediatric anaesthesiologists everywhere to perform routine pro-

cedures such as imaging examinations or ambulatory surgeries.'

Spain is the leading country in organ donations worldwide. What are the main issues for the anaesthesiologist in this context?

'My hospital is among the first three hospitals in Europe to perform lung transplants; we carry out 50 operations a year and have treated 700 patients so far.'

'Spain performs a lot of transplants and there is an impulse to open new centres; this is quite controversial. If you want to maintain a high level of care, you should only have a low number of centres carrying out transplants.'

Specialization is needed because ventilation is different in children and they respond differently to anaesthetics



Do you programme a ventilator individually for each patient?

'After 20 years' teaching and giving training all over the world, I have come to realise that most countries do not have deep knowledge of mechanical ventilation. Ever since Siemens introduced the "green points" on the screen of ventilators to help anaesthesiologists and intensivists, we have been setting all the ventilators exactly the same way for everybody. Furthermore parameters are not changed every day according to the state of patients' lungs.'

'In Europe, things are changing. We have to set ventilators individually because patients are unique. A smoker's lungs are not the same as a non-smoker's. Programming ventilation also depends on the position of the patient.'

'Ventilators now offer much more information. They deliver volume, pressure and flow time curves in real time breath-by-breath, pressure volume loops, etc. All these tools give you specific information on respiratory function. We now have to interpret and analyse this information to know how to ventilate each patient individually.'

'We have to train our colleagues accordingly. This is one of the biggest challenges in our field.'

What are the latest developments in anaesthesiology and critical care?

'Intensive care technology has developed rapidly over the past decade and these advances have made their way to anaesthesia practice. Ventilators are just as good in both fields, but most anaesthesiologists are not familiar with these tools yet.'

'Cardiorespiratory mechanical support devices provide heart and lung function artificial support. These machines are coming to the market; there are two or three new cases per month. They are the future.'

'Neural adjusted ventilation assist (NAVA) technology enables mechanical adaptation of ventilation to the patient's diaphragm; this will play a significant role in the years to come.'

Does automation or learning software play any role in your discipline?

'Everybody has been looking into automating everything for the past decade. The problem is that mechanical ventilation is a disregarded field. Efforts have focused on creating software that everybody can use, so that no one has to do mechanical ventilation any more.'

'Software is helping clinicians, but is not solving problems. So far this has not been working at all. Using software requires programming for each patient; software cannot run on its own. Some patients will want to breathe in two seconds, others in three or more. Clinicians need to adapt to each individual patient.'

'We have to see what the future can offer and whether automation can help us in complex situation like asynchronies, recruitment manoeuvres, weaning, etc.'



From left: paediatric anaesthesiologist Patrice Bourgeois, Javier Garcia Fernandez and a resident at La Paz Hospital

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Meta-analysis of Home Monitoring trials TRUST, ECOST and IN-TIME shows the reduction of all-cause mortality in an unselected patient population

* Hindricks G et al., Daily remote monitoring of implantable cardioverter-defibrillators: Pooled individual patient data from IN-TIME, ECOST, and TRUST trials suggest a mechanism of clinical benefit, ESC Congress 2016, Rome.

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PROFILE: Tomasz Grodzki

Polish Senator and pioneering lung cancer surgeon

Report: Magdalena Mariankowska

Poland, 2016 – First thing on a recent Monday morning, Professor Tomasz Grodzki could be found performing a lung resection in an operating theatre at the Pomeranian Medical University. Just two days earlier he was in a meeting with Senator John McCain, in Washington D.C. For this professor is not only a leading lung cancer expert, heading the General Thoracic Surgery Department in the Regional Hospital for Lung Diseases; but he was also elected (2015) to the Senate of the Republic of Poland.

Born in Szczecin on 13 May 1958, 25 years later he graduated in medicine from the town's Faculty of Medicine in the Pomeranian Medical Academy (Now the Pomeranian Medical University).

As a young graduate he was among student activists championing a programme that endorsed an anti-communist platform and drew from an anti-Marxist stance calling for national sovereignty and independence, as well as free elections, albeit with economic reforms. 'I can still remember painting anti-Communist slogans in Szczecin', Grodzki recalled, when speaking a month ago with a group of people marching in Warsaw to protest against Poland's conservative government – 27 years after communism fell.

This period in his young life was not mainly about student unrest and politics, however. He gained a specialisation in general surgery and then in general thoracic surgery and clinical transplantation and, in 1983, had begun his career as an intern at the Provincial Centre of Occupational Medicine in Szczecin. In the following year he joined the Regional Hospital for Lung Diseases



in Szczecin-Zdunowo, becoming director of the General Thoracic Surgery Department in 1995.

1996 – a landmark year

At his Thoracic Surgery and Transplantation Clinic, Grodzki lead his handpicked surgical team in performing Poland's first lung transplant. The year was 1996; their procedure solidified the Clinic's reputation as a leader in lung transplant surgery.

20 years on, Grodzki vividly remembers that medically historic event, recalling the key emotional moments when the donor lung was placed, blood vessels re-attached,

and the donor lung successfully re-inflated for the first time.

In 1998 he became CEO of the clinic and, since 2003, he has led the General Thoracic Surgery and Clinical Transplantation Clinic at the Pomeranian Medical University in Szczecin.

Thanks to medical progress and close supervision by the professor's highly specialised, multidisciplinary team, nowadays the clinic's survival rates after lung transplantation are comparable with results from other leading international centres.

Politics, however, has remained an important subject for the surgeon. Thus, from 2006, up to last year,



he also served as a Szczecin City Councillor.

'I've spent over 30 years in medicine, from medical university, through research and active clinical practice of lung cancer surgery and lung transplantation, serving patients one by one. But through politics I can serve many at one time,' Grodzki explains.

Superhuman

When people heard he sought to run for the Senate, yet remain in the one of the most highly specialised medical fields, none reacted with disbelief. They recognised that no task is too large for the surgeon and there is nothing he is not capable of handling. He is perceived as a multi-tasker, achieving what ordinary humans cannot comprehend.

The winning team of thoracic surgeons (pictured above) he has developed at his Szczecin clinic in Zdunowo Hospital is also recognised worldwide for quality and innovative strength. An important reason for this is the public and private investment in training and further international education of the medical professionals.

Grodzki ensures that the team's pneumologists and thoracic surgeons are continuously involved in research and international development projects on next-generation medical applications in diagnosis, management and treatment of lung disease. Thus, the experts routinely perform many very complex procedures on international patients,

treating a full range of respiratory disorders such as asthma and allergy, lung inflammation and cystic fibrosis, lung infection and immunity, lung failure (including transplant, COPD and sleep ventilation), cancer services and lung assessment.

'Whenever medical treatment is necessary,' the team believes, 'sensitive, reliable and efficient care should always be ensured without any delay or bureaucratic hurdles.'

Emphysema revolution

In another field of interest – severe emphysema – treatment includes a somewhat revolutionary new treatment for patients – lung volume reduction coils. In summer 2015, this was introduced for the first time in Poland at Szczecin Zdunowo Hospital. The approach uses a bronchoscope to place elastic wires into areas of damaged emphysematous lung. The wires coil up, restoring tension to the lung and holding the airways open to allow air to leave when the person breathes out.

Annually, the thoracic surgical team performs more than 1,000 major thoracic procedures, including lung transplants. The physician/scientists within the clinic also pursue a wide range of projects, including bench, translational, and outcomes research focused on pulmonary diseases.

Do they relax? Extreme sports enthusiasts – every winter, they-whooosh down the Dolomites' serious slopes.



A professor of medical science since 2010, Polish Senator **Tomasz Grodzki MD PhD FETCS**, heads the Thoracic Surgery and Transplantation Department at the Regional Hospital for Lung Diseases in Szczecin-Zdunowo, Poland. He is also National Consultant in Thoracic Surgery for Poland and Chairman of the Polish Society of Cardiothoracic Surgeons. Grodzki's main research interests include lung cancer screening and surgery; lung function following resection; technical modifications; lung transplants and case reports; oesophageal cancer; and LVRS including intrabronchial valves and coils. He is a past-President of the European Society of Thoracic Surgeons (2003–2004) and is the first Polish member of the American Association for Thoracic Surgery. From 1997–2014 he was deputy chairman of the Council of the Transplantation Aid Foundation in Szczecin.

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The best prophylaxis against post-surgical wound infection

The importance of suture material

Report: Bettina Döbereiner

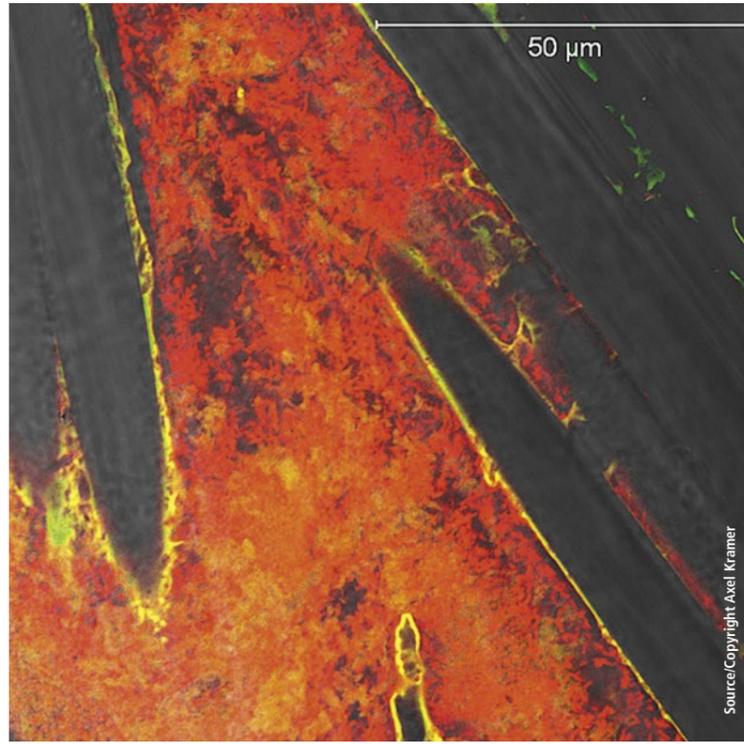
Wound infections after surgery are not uncommon and can be fatal. In Germany, postoperative wound infections are now the most common type of hospital acquired infection (HAI), with a proportion of 24%. An expert on infection prevention and control, Professor Axel Kramer, who directs the Institute for Hygiene and Environmental Medicine at the University of Greifswald, Germany, believes that suture material may be an underestimated aspect of prevention.

Postoperative wound infections are typical complications that occur after surgery. They typically develop through entry of pathogens, mostly bacteria, via the skin or mucous membranes into the surgical site.

According to the Hospital Infection Surveillance System KISS, 1.6 out of 100 surgical interventions in German hospitals lead to surgical site infections; this results in some 267,000 postoperative wound infections annually (2014 figure).

These are only estimates – precise data is lacking. However, the fact is that some of these nosocomial infections could be prevented – between 20-60% of them, Kramer estimates. In terms of the total number of post-operative wound infections annually this would represent between 53,000 – 160,000 fewer cases.

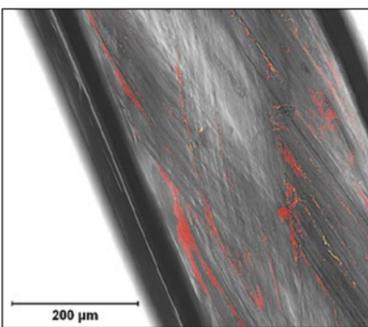
How best to prevent SSIs is one of Kramer's specialist research areas. At the 4th Forum on Infection Prevention and Control held by the German Medical Technology Association (BVMed), in Berlin last December, he explained his recom-



Comparison between Triclosan impregnated suture and two non-impregnated sutures. After 12 hours, the non-impregnated sutures were colonised with an initial biofilm, which developed its full growth after 24 hours.

mendations for the best options of prevention.

His urgently recommended strategies to tackle SSIs include eradication of existing infections before elective surgery, standardised pre-operative skin antiseptics, sterile covering of the surgical area, no shaving (if required then clipping instead of shaving), aseptic, tissue-



conserving working methods, sterile clothing, surgical hand disinfection, intact surgical gloves (if necessary double gloving), surgical masks and

perioperative antibiotic prophylaxis (PAP) and – to complement all this – the respective suture material.

Underestimated implants

The surface of a conventional, sterile suture (braided vicryl) with a length of 150cm has, Kramer calculated, the same surface area as the side of a CD cover. 'This means that, during the formation of a biofilm, around 325 billion pathogens can colonise this area and, in the case of multi-layer biofilms even up to a trillion pathogens,' he explained. 'The suture material is in fact an implant, but unfortunately often not recognised as such,' Kramer points out.

This implant bears the same risks as other implants. The number of pathogens required to cause infection is far lower around the suture material. Therefore, the probability of infection via the suture material, particularly in body areas with high bacterial colonisation, such as the colon with its complex intestinal flora, is markedly high. It is also possible, Kramer says, that a biological film may form around the suture and thus protect the pathogens from immune defence. The suture can almost act like a 'slide' into deeper layers of tissue and cause infection there.

Triclosan coated sutures

Kramer therefore recommends the use of antiseptic-impregnated suture material, particularly for visceral surgery. The number of SSIs here is significantly higher than the average 1.6, at 9.36 per 100 surgical interventions. However, even if all measures of prevention are adhered to, invasion of pathogens, such as from the intestine, can never be completely prevented even with antimicrobial suture material, Kramer emphasised.

Currently, the only antimicrobial suture material available is coated with the antimicrobial substance Triclosan. Impregnation with Triclosan prevents the biofilm development on the suture



Professor Axel Kramer MD is a specialist in Hygiene and Environmental Medicine and former head of the Institute for Hygiene and Environmental Medicine at the Ernst-Moritz-Arndt University Greifswald, Germany. In this role he combines teaching with research, as well as the management of infection prevention- and control for the University Hospital Greifswald. He is a member of the commission for 'Hospital Infection Prevention- and Control at the Robert Koch Institute' and a founder member of the German Society for Hospital Hygiene (DGKH), having been its president from 1990 to 2010.

material. However, there is a gap in effectiveness against the fourth most common cause of SSI, P. aeruginosa. However, irrespective of this, the benefits of antimicrobial suture material continue to be controversial.

For abdominal surgery, four meta analyses now confirm a reduction in the SSI rate through the use of Triclosan-coated sutures. However, a PROUD study showed no significant impact on superficial (A1) or deep (A2) surgical site infection after elective, median abdominal laparotomy. However, says Kramer, after consolidating the data from the PROUD study with data from four further studies it was possible to document clear superiority of the antiseptic suture material (Diener et al 2014). Potentially positive results have so far also been achieved in breast cancer surgery and heart surgery.

For Kramer the trend, at least for abdominal surgery, is obvious, even though more proof is still required. He is convinced by the benefits. The University Hospital Greifswald has therefore been using antibacterial suture material since 2005.

Self-control with checklist reduces SSI rate

Irrespective of the research situation it is obvious that only a combination of a whole bundle of measures will lead to success in the prevention of wound infections. Kramer therefore suggests specific bundles of measures to combat SSIs, which each surgical department should establish, train its staff in and then monitor. At the Centre for Colon Cancer, in Greifswald, this has been successfully implemented since 2009. Surgeons control adherence to all-important measures of prevention via a checklist prior to commencing surgery. This has led to a stable reduction of superficial (A1) and deep (A2) SSIs by an average of 60% in the period between 2011 and 2015, Kramer says.

Conclusion:

If postoperative wound infection was to be reduced by more than half through suitable measures of prevention, such as seen in this example from Greifswald, based on the aforementioned prevalence rate in Germany this would save a total of €1.8 billion – but most importantly it would spare many patients the unpleasant and sometimes even deadly effects of wound infections.



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