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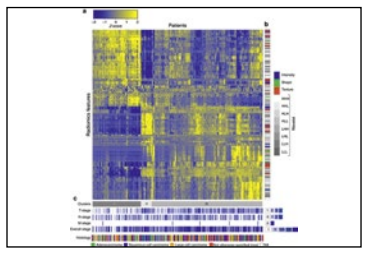

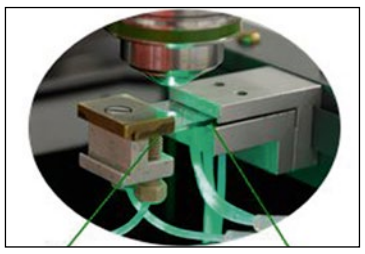

Go girl! Go!

Achieving equality in healthcare upper management

Interview: Jane McDougall

France has 32 hospital groups – two regional hospital groups (CRH) and 30 CHUs. Ranked among the 10 best hospitals in France, The Rennes University Hospital (Centre Hospitalier Universitaire [CHU] de Rennes) employs 7,700 people (the second largest employer in the region) and processes almost 1,500 hospitalisations every day. Untypically, since 2015 the general director has been female: Véronique Anatole-Touzet. 'When I was first appointed to a regional director position at the Metz-Thionville regional hospital in 2007,' she said, 'I was one of only two women to head a large hospital group.

'Since I've been at Rennes, thanks to positive pressure to achieve equality in the upper management of government-run bodies, including healthcare, which started under President Hollande and is continuing under President Macron, consecutive health ministers have succeeded in bringing this number to 12, which is nearly 40%, and can be considered a great achievement.'

Why are so few women in these top positions?

'One of the barriers to women obtaining a directorship is that the selection panels, who draw-up the short lists, are men. Department heads are men; only about 15-20% of higher management posts in hospitals are filled by women, so traditionally the lists of six candidates would be all male. However, that has changed legally now and equal numbers of men and women must be short-listed, which already puts women in a better position because they are at least considered for a position.'

With equal or higher numbers of women studying management and medicine, why do so many fail to reach the highest echelons of the profession?

Source: Shutterstock/Monster Ztudio

'The situation is not a straight forward numbers game. There are multiple reasons why women don't get these positions. Women tend to be their own worst enemies. Broadly speaking, they are far more open to self-doubt then males in equivalent posts, they are the first to self-criticise and consider their efforts below the required standards. Blaming themselves for failure that is not of their making is also not uncommon. This is in addition to the fact that careers in higher management tend to open up when we are in our late 30s to early 40s. This coincides with the time that women have young children, possibly of school age but requiring care after school, too young to be left at home alone. Even with good childcare in place, women are openly criticised and made to feel guilty for abandoning their families for their careers. Or maybe they feel that by becoming a mother that is enough responsibility in their lives and they are happy to work fewer hours and not have the stress of upper management, as well as balancing home life, holidays and childcare against a background of hostility even if it is well hidden.'

How can we overcome this?

'Women need to be sure of their abilities, educated to a similar level they are every bit as good as a man in a similar role. In fact, it could be considered – again broadly speaking – they may be better managers, more open to listening, less egotistical, better at compromise than their male counterpart, again I insist these are personal characteristics and there are men that display these characteristics and many women who are arrogant and poor listeners but on the whole these gender stereotypes do seem to exist in the hospital environment.'

What can be done to improve things?

'Improvement has to come from the whole environment. For a woman to succeed there has to be a support mechanism in place to allow her success. Not just in the workplace but at home; husbands need to support their partners to enable them to progress with their careers by taking on their share of home and childcare. We know from repeated reports that women still do the majority of this despite working full time.

'France may be better than some countries in having more equality in terms of childcare facilities and men doing their share but, at the end of the day, we are still a "Latin" culture with the undercurrent of machoism that accompanies it. Also in a couple there has to be agreement, to climb to the top often means moving town, even region. This can again be exceedingly difficult without the support network needed from schools, childcare facilities, partners, family and friends. Things are changing, but slowly.

'The only way to create a climate of true equality is for everyone to work together, men and women, to reduce the burden of guilt on the shoulders of a working mother. We can become more flexible in working hours, not organising meetings for late afternoon; being understanding when a woman needs time off for childcare/illness etc. Flexibility in the working day/week even, allowing women to have the time needed to retain the correct balance between personal and professional life. Within the hospital, teams should think about each other, cover for one another and step up when needed. This requires education of men primarily, to consider their role in family life, but also other women to be helpful and non-critical of a colleagues needs.'

'There is also the 'me-too' movement which has changed the way women are treated in the workplace. Men are, as a rule, more respectful of their female colleagues, sexual innuendo and misplaced comments (however, jokingly implied) are no longer tolerated. In fact, many of the younger generation of men in the medical profession would not dream of behaving in such a way. Ten or 15 years ago, sexist comments were commonplace and considered something women had to put up with. This is no longer the case. Any disrespectful behaviour is sought out and stopped at source, however senior the perpetrator.'

What advice would you give the new generation of directors?

'Dare. Have the confidence to step up and seize what's available to you. It will be hard but, rather than stop in an assistant director post, learn and move on. You can do it, go girl!'

A graduate of the Institute of Political Studies of Paris and the School of Advanced Studies in Public Health, **Véronique Anatole-Touzet** worked, from 1986 to 1998, for the Public Hospital Group in Paris (APHP). There she contributed to the development of the group's strategic plan, before serving as Director of Finance and Information Systems at the Bicêtre CHU. Still with the APHP, she was promoted to Head of Department for Foresight and Employment, before taking up management of the Eure-Seine Intercommunal Hospital, in Higher Normandy. From this position she was appointed General Director of the Metz-Thionville Regional Hospital Centre in 2007 and then finally, to her current role as General Director of the University Hospital Centre in Rennes, in March 2015. She is also a Knight of the National Order of Merit and a Knight of the Legion of Honour.

Altering the culture of male prevalence

Getting to the top, staying feminine

Women continue to lead a rather marginal existence in medicine. Although there are now more female than male medical students, professorships and directorships are almost exclusively held by men. This imbalance was addressed with the lecture series 'Women in Focus' at the 2019 European Congress of Radiology (ECR), the annual meeting of the European Society of Radiology (ESR) held in Vienna. The organiser, Professor Hedvig Hricak, invited top-class participants to speak about the gender gap – and not only women could learn a lot from the contributions made.

'Taking on a leadership position is always quite a decision,' Professor Hedvig Hricak underlined, during a recent ECR lecture. This applies to both genders – so why is it so much rarer to see a woman at the top? Inherent physical and even psychological differences affecting women were discussed but quickly discounted as untenable. A more likely reason could be that women often hesitate rather than take the

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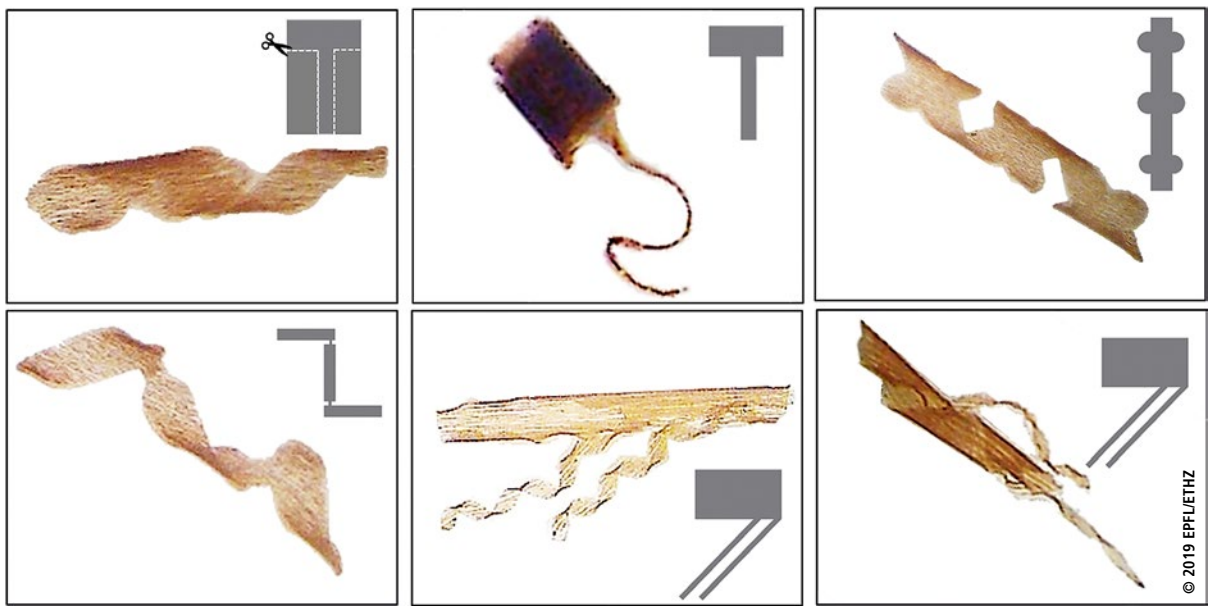
Research: Microrobots to re-shape drug delivery

Transforming minuscule 'swimmers'

Scientists have developed minute flexible robots that could help revolutionise drug delivery in the future, Mark Nicholls reports. These 'microrobots' are so small that they could be ingested, or inserted into human veins to deliver drug therapies directly to diseased body areas.



The microbot project is still very much at the research stage, but scientists masterminding the research at ETHZ (Swiss Federal Institute of Technology Zürich) and EPFL in Lausanne are confident it has enormous potential in the delivery of specialised treatments. The highly-flexible biocompatible microrobots – or microswimmers – have been developed by scientists led by Professor Brad Nelson at ETHZ and Professor Selman Sakar at EPFL.

With tiny magnets within the design, the machines – which vary in size from a few millimetres down to less than a millimetre in total length – can swim through liquids and change shape as needed to move through narrow blood vessels and intricate systems.

Additionally, the microswimmers can be of different shapes or stiffness to reflect a specific task, with the study team following a variant of origami, called kirigami, to design and fold compliant 3-D microstructures from a thermo-responsive gel composite reinforced with micronanoparticles.

In the robot design, Nelson, who is Professor of Robotics and Intelligent Systems in the Department of Mechanical and Process Engineering at ETHZ, said: 'We were inspired by tiny microorganisms, like bacteria, which can change their shape to escape physical traps. To control and manoeuvre them, we embed magnetic particles in the materials and then externally generate magnetic fields to create forces on them to propel them through liquid.'

To create the robot devices, the team used stimuli-responsive hydrogels made of N-Isopropylacrylamide and polyethylene glycol diacrylate with iron-oxide magnetic nanoparticles embedded within them. The magnetic nanoparticles allow them to be controlled via an electromagnetic field, though the microrobots have been designed in such a way that they can also utilise the fluid flow to navigate on their own through cavities.

In their findings the researchers suggest that the 'development of microscopic artificial swimmers that can cross biological barriers, move through bodily fluids, and access remote pathological sites can revolutionise targeted therapies.'

Professor Nelson added: 'In nature, there is a multitude of microorganisms that change shape as their environmental conditions change. We have been inspired by this basic principle in the development of our microrobots.

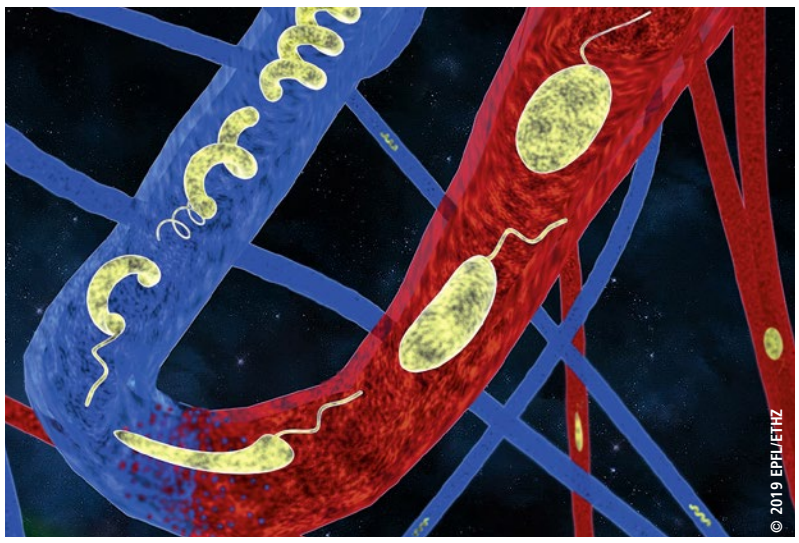
'The key challenge for us was to develop the physics that describe the types of changes we were interested in, and then to integrate this with new fabrication technologies,' he pointed out adding that, in terms of healthcare, particularly in respect of targeted drug delivery, 'They are able to swim through tortuous blood vessels to deliver drugs, for example to unblock a thrombosis or to fill an aneurysm.'

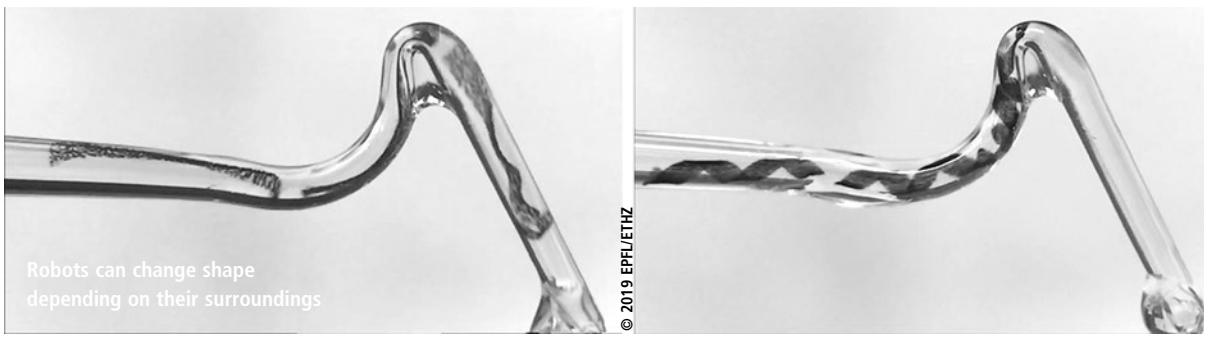
Additionally, Sakar, Assistant Professor in the Institute of Mechanical Engineering at EPFL, said: 'Our robots have a special composition and structure that allow them to adapt to the characteristics of the fluid they are moving through. For instance, if they encounter a change in viscosity or osmotic concentration, they modify their shape to maintain their speed and manoeuvrability without losing control of the direction of motion.'

While currently at the research stage, the next step for the scientists is to test them in ex vivo animal tissue. However, they remain confident that their robots can be inexpensive and be manufactured relatively easily.

Brad Nelson has been Professor of Robotics and Intelligent Systems at ETH Zürich since 2002, conducting research on microrobotics, nanorobotics, and medical robotics. His key interest lies in how to make tiny intelligent machines of millimetres to nanometres size, with applications in medicine. Nelson was an Assistant Professor at the University of Illinois at Chicago and an Associate Professor at the University of Minnesota before moving to ETH. With over 30 years of experience in the field of robotics, he has received numerous awards for his work in robotics, nanotechnology, and biomedicine.

The robots are modeled after bacteria and fully biocompatible





Getting to the top, staying feminine

Continued from page 1

initiative. 'Nobody can read your thoughts. Always communicate your views and ideas openly, otherwise you will not achieve your goals.' The ability to see a counterpart's perspective is just as important. 'Whoever says that a woman has to put her career before her family, or the other way around? Everybody has to go their own way – and this must be respected.'

Proof that his advice actually works was delivered by Cally Palmer, National Cancer Director and one of the top post holders in the British (NHS). 'Resilience is essential, especially around fundamental principles,' Palmer underlined. 'But, it's just as important to know when you have to be flexible and to make concessions if you want to reach your goals.' Those who will not stand in their own way through either a lack of self-confidence, or an inflated ego, can likely hold their own at the top – no matter whether male or female.

Catherine Estrampes

Cally Palmer

Hedvig Hricak

Success through empathy, not aggression

This was also confirmed by Catherine Estrampes, president and CEO of GE Healthcare in Europe, who spoke of success in the business world. 'In the course of my career,' she said, 'I've seen many women in leading positions who behave in a stereotypically male manner: they are pointedly aggressive and happy to take risks because they believe this is the only way to succeed. But that's not true. One of the most important abilities is to look after and care for others – often described as a "feminine" trait. But we all have this ability – not only women.'

Diversity comes up trumps in tomorrow's radiology

Congress president Professor Lorenzo Derchi was optimistic about the future of women in radiology, and said, in self-mockery: 'Today, leading positions are mostly held by old men like me. But this culture of male prevalence is already being shaken up, and in a few years' time many of these roles will be filled by women. Radiology can only benefit from the end of this inequality.' (WB)

The 'Women in Focus' sessions were held near the congress centre, in The Church, impressively redesigned by Austrian set designer Amra Berman Photo: Behrends

Wanted: better rural care, multidisciplinary teams, telemedical structures

Cancer prevention scrutinised

The latest study by the German Society for Haematology and Oncology (DGHO), 'Prognosis for population-based morbidity for common cancers in Germany – impact on provision' has made it clear that due to demographic developments in Germany and to medical advances in oncology, the requirements for cancer patients' care are ever more diverse. The increase in newly diagnosed cancer patients is likely to be around 10%. The number of people living with cancer and those cancer patients with chronic concomitant diseases will also increase significantly. The current figures revealed in the study suggest important conclusions for the country's health politics.

For its study, Germany's DGHO used different data sources, such as population registers and epidemiology cancer registers. It shows the predicted development of important parameters such as the number of newly diagnosed cancers and prevalence right down to regional level. 'This enables very precise and differentiated statements on trends in cancer care in this country, which would otherwise not be that obvious,' emphasised Professor Carsten Bokemeyer MD, Chairman of the DGHO.

The analysis only included audited cases, meaning that an overestimation of the initial figures is unlikely. According to estimates from the Robert Koch Institute, not all federal German states achieved the required reporting rates of 90% for the entities in 2014. It is therefore assumed that the figures for incidence as well as for the resulting prevalence are likely to be slightly higher than those stated in the report. Possible regional developments not caused by age structure and gender ratio were disregarded. New therapy approaches and innovative treatments that will lead to an improvement of the survival rate were also disregarded.

The most important results of the study were summarised concisely by Professor Wolfgang Hoffmann MD, who conducted the study. All projections are based on the demographic development of the German population. It is assumed that the country's overall population will increase by around 1.3 million people between 2014 and 2025.

However, this will not happen evenly across all age groups. In fact, it is expected that the number of men and women aged 60 and above will increase by 21% and 15% respectively. Among men and women aged 80 and above, the increase is likely to be as much as 51% and 26% respectively. In absolute figures this is an increase of 1.6 million in 2025 compared to 2014. This goes hand in hand with a decrease in the single digit percentage range of the number of those aged between 10 and 59 of both genders.

Age-related tumours will therefore become more common, and the complexity of cancer cases will increase for many patients. Looking at the most common cancers, the following prognosis can be made: The number of newly diagnosed cancers between 2014 and 2025 will likely increase by 10%, meaning that, in 2025, there will be more than 520,000 cases per year. For men, the biggest increase will be seen for prostate cancer and, for women, breast cancer will increase the most with old age.

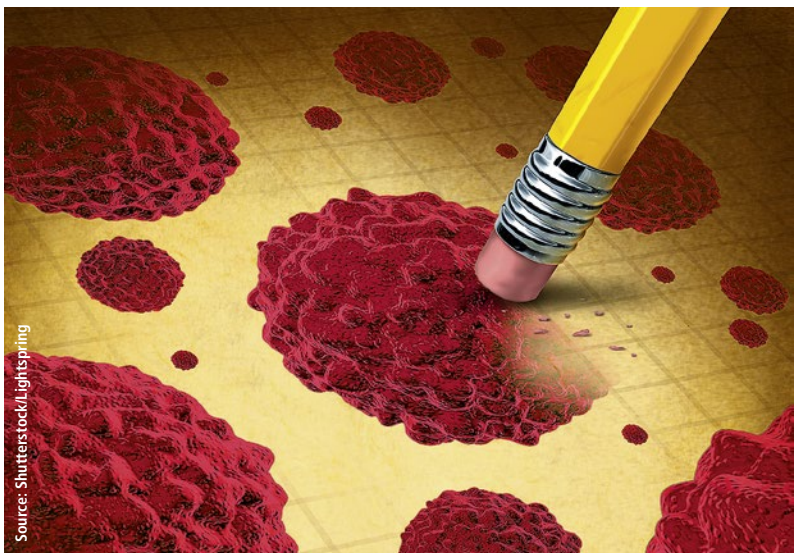
The 10-year prevalence of cancers will increase considerably between 2014 and 2025. An increase of around 8%, to almost three million patients, is expected.

The number of patients who suffer from at least one further chronic disease alongside their cancer is also expected to rise significantly. The study used the figures for cancer patients who also suffer from diabetes mellitus, chronic obstructive pulmonary disease (COPD), coronary heart disease, obesity, renal insufficiency or dementia at the same time for these calculations.

From left to right: Prof Carsten Bokemeyer MD (DGHO), Ingo Tamm MD (BNHO), Maike de Wit MD (ADHOK) and Prof Wolfgang Hoffmann MD (University Hospital Greifswald, Germany)

An improvement in care structures in rural regions is urgently required. Clearly, the number of older people living in rural areas will be disproportionate. Against this background it is to be expected that the requirements for specialist cancer treatment will increase. 'It's clear that the requirement for specialists over the next few years will grow due to the rising incidence and increasingly complex treatments.

'We need to establish structures of provision that make the competence in specialised centres available comprehensively, if we don't want to risk entire regions, or the aged, being left behind when it comes to cancer care,' emphasised Professor Maike de Wit MD, of the Working Group for Haematologists and Oncologists in the Hospital e.V. (ADHOK). It would therefore be beneficial to see a further delegation of medical services and more efforts towards the implementation of Medical Care Centres (MVZ) in community hospitals.



It also became clear that high quality, outpatient cancer care must be made available comprehensively. 'Comprehensive and optimal cancer care requires concepts which integrate cancer care,' said Ingo Tamm MD, of the Professional Association of Haematologists and Oncologists in Germany e.V. (BNHO). The increasing cancer prevalence is a particular challenge. 'Very good treatment options for chronic myeloid leukaemia (CML), for instance, have led to a greatly increased prevalence of these patients – 20,000 and more in the next few years. We must provide outpatient oral treatment for them in the best possible way,' Tamm said.

The increase of comorbidities leads to a more complex situation for outpatient care. Cancer patients must be treated more individually, must be monitored more closely with regards to recurrences and, in the advanced stages of the disease, must be given the best possible palliative care. With this complexity in cancer treatment and provision, haematologists and oncologists working in outpatient care are playing key roles alongside specialist cancer centres. Therefore, it is important that these specialists are supported by specialised cancer nurses, palliative care teams, as well as trained general practitioners. Telemedical care should also be extended.

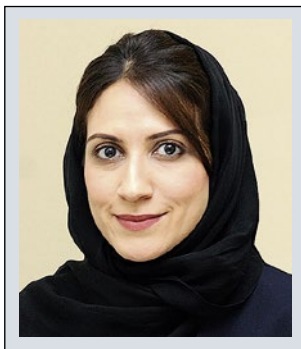
'The results of the DGHO study are not least an appeal to all of us and to politicians to advance cancer prevention,' Bokemeyer emphasised in conclusion. 'Cancer risk increases significantly with age, but it is not unalterable.'

Source: Prognosis of population-based morbidity for common cancers across German and the impact on provision. DGHO position paper on the challenges caused by demographic changes for future requirements in oncological care in Germany

Aiming to drive health investments in Dubai

Dubai's notable healthc

Formed in 2007 – under the directives of Sheikh Mohammed bin Rashid Al Maktoum, the Vice President, Prime Minister, and Ruler of Dubai, UAE – the Dubai Health Authority (DHA) oversees the healthcare system. Driven by the private sector, the country's healthcare growth is a notable success story. Daniela Zimmermann, of European Hospital, asked *Dr Ibtesam Al Bastaki*, Director, Investments & PPP's at DHA about the vision for future healthcare.



Dr Ibtesam Al Bastaki, Director for Investments & PPP's at DHA

Dr Ibtesam Al Bastaki: Dubai's healthcare landscape has developed significantly over the past decade and will grow even more specialised in the future. We have the factors that fuel the growth of demand and utilisation of health services and, with the support we offer investors, we have a healthy future. In this, the Government can work closely with the private sector to develop and support a robust and sustainable health system that delivers a good patient experience and high quality outcomes, while supported by clinical innovations and evolution of technological evolution that will re-shape future healthcare systems.

The drive is to establish advanced medical capabilities and modern infrastructure and facilities in the city, to make Dubai an attractive destination for private sector investment, which also supports the city's ambition to grow in profile as the leading medical tourism destination in the Middle East.

What challenges does Dubai face to provide the best national healthcare?

Demand for quality health services is increasing due to Dubai's rapid urban development, population growth and the influx of medical tourists, which is a big opportunity for private sector providers and investors in the health sector.

Many of world's largest hospitals and specialised centres have invested in Dubai's healthcare sector after realising the city's unique investment climate. We are seeing a growing need for primary care services for some population segments and communities, and thus we need to look at innovative models in primary care, such as walk-in clinics for urgent care and ambulatory care centres; there's a lot of interest and new investment in these models. We also need to embrace and support the role of telehealth to enhance and integrate with primary care services, which will help curb over-utilisation and support efficiency.

Considering Dubai's pace to gain a high-level healthcare infrastructure, what could draw European investors into a long-term engagement?

We believe lessons can be learned from successes and challenges within health system transformation in countries in the East and West. We believe no health system is perfect – each has its unique strengths; there are elements that work really well and come together nicely, and other areas where a health system faces challenges. We believe we can learn a lot from health systems that have ensured sustainable private sector investment in healthcare, and those that are implementing value-based healthcare models along with a transformation in the reimbursement of care through outcome-based and capitation-based models, that help to ensure improved quality and clinical outcomes, and help curtail and limit the growth in healthcare spending. This is a critical challenge because the population ages and the number of chronic diseases continue to grow.

We believe investors and private sector providers need to understand the dynamics of the Dubai Health System from the regulatory framework and licensing processes, the demographic profile and income segments, epidemiology and disease profiles, health investment needs and gaps in the reimbursement framework and insurance market, which is different from the health system they know.

What can be learned from European healthcare and what can Europe learn from Dubai?

Clearly, lessons can be learned on developing an efficient and adaptable infrastructure. There's a lot of innovation, and technology is changing how healthcare is delivered to patients. It is patient centric and value-based; effective measures are taken to appropriate health investments and to achieve better clinical outcomes and efficiency, and avoid over-utilisation of services, which is unsustainable and pressures the Government, businesses and the individuals who pay for these services. There are great examples of integrated models of care, development of centres of excellence and in using technologies to better monitor those with chronic conditions and provide remote patient management, which will all be studied as we develop our health system.

Other countries can also learn from our piloting of many innovations and technologies through the Dubai Future Accelerator program. We are open and welcome international investors and providers. Dubai is ranked among leading destinations with an ease to set up and operate a business, and we have perhaps the greatest diversity in the workplace compared to several other countries, because people from all over the world have made Dubai their home.

What is the rationale behind the investment guide?

The overarching aim of the Dubai Health Investment Guide is to provide investors with real-time, reliable and robust information on demand for health services, supply and capacity gaps, and to enable investments in strategic opportunities and specialised health services. This benefits Dubai's economy and the health sector because it helps to optimise and balance the supply of health services, informing investors clearly about areas of overcapacity, and quantifying the gaps where investment is needed. The investment guide is broken up into different segments:

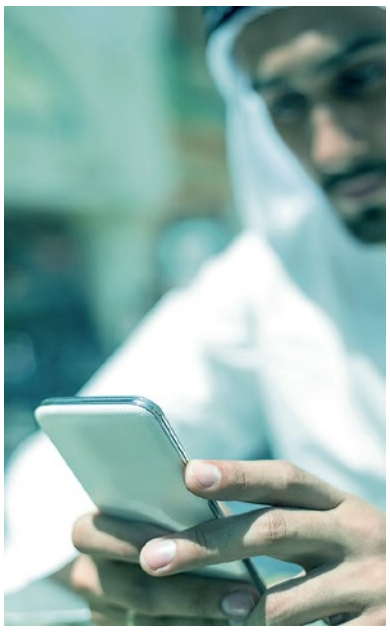
- It details the drivers underpinning the growth of healthcare demand in the Emirate of Dubai, which includes the growing population, strong and diversified economy, stable and attractive investment climate, rising burden of disease and prevalence of chronic diseases, rise in health tourism among others
- The guide provides an overview of health regulations and the health insurance system which

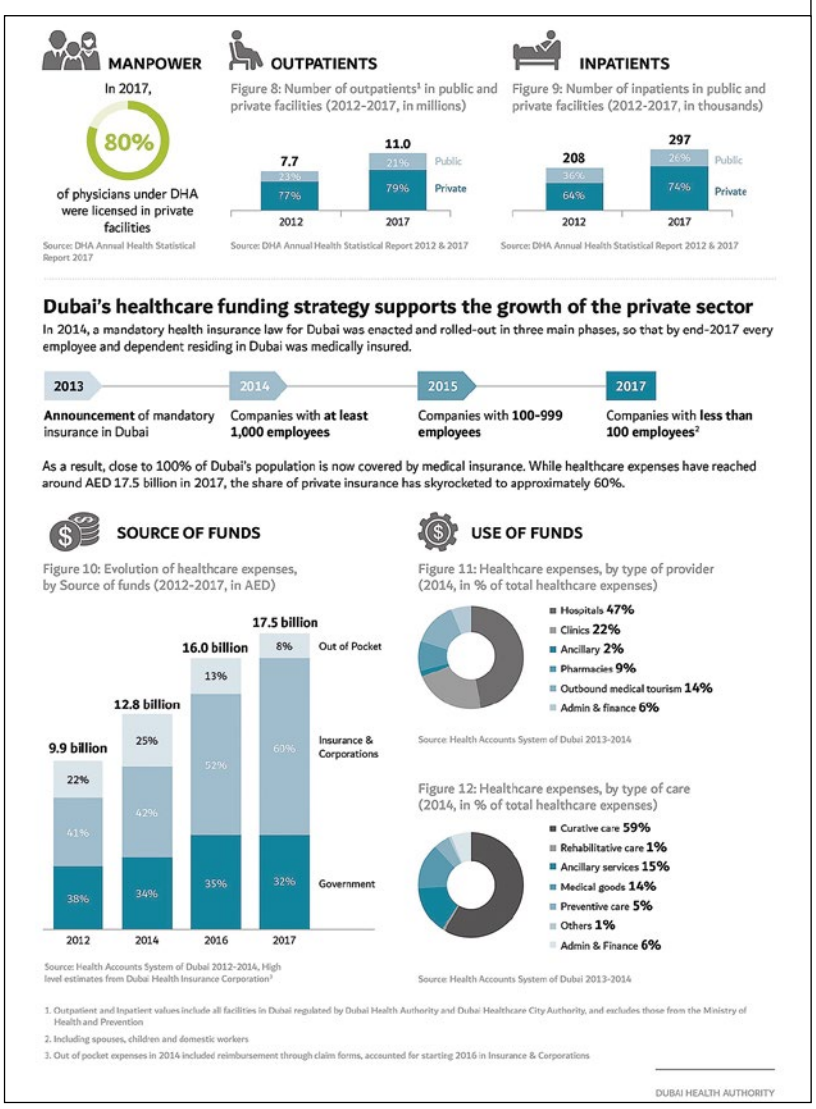
DHA's investment focus for the next 2 to 3 years:

- Innovations in primary care
- Ambulatory care
- Urgent care clinics
- Mental health
- Chronic disease management
- Tertiary care for diabetes, cardiology and oncology
- Diagnostic health and remote monitoring
- Rehabilitation and physical therapy
- Home-based care
- Long-term and extended care

DHA's investment focus for the next 3 to 5 years:

- Prevention and pharmacy beyond-the-pill
- Precision medicine and genetics
- Population health management
- Nursing homes and palliative care





care

includes upcoming changes and initiatives relevant to investors
- The investment journey for different types of facilities is mapped
- Investment needs and priorities are highlighted for outpatient care units, acute inpatient beds and specialised services, including long-term care and critical care beds for 2020, 2025 and 2030, based on the Dubai Clinical Services Capacity Plan 2018-2030
- Details are given of 'free zones', focused on supporting healthcare and life sciences

What opportunities in the healthcare ecosystem does the Dubai Health Investment Guide identify?

In the short term, 3-4 years are needed for the continuum of care – to develop and enhance services for chronic disease management, developing Centres of Excellence for cardiology, oncology, diabetes and other specialties, to enhance and improve access to long-term care, physical rehabilitation and home-based care, particularly to support the needs of the elderly and others with special needs in our Emirate, and to enhance and improve access to mental health services. Long term, we want to focus much more on population health management, value-based care supported by better clinical outcomes and efficiency for the health system, improvements and adoption of genetic medicine and precision medicine, and beyond-the-pill-initiatives. We are very focused on supporting the emergence of urgent care clinics, ambulatory care, specialised centres for different diseases and specialties and the use of telehealth in primary care and remote patient monitoring.

Taiwan's holistic healthcare concept

Between high-tech and tradition

Within a groaning 140-tonne particle accelerator a patient receives proton therapy, whilst down a few corridors, acupuncture needles are being placed and herbs mixed. 'Tradition and high tech walk hand in hand in Taiwanese healthcare,' EH correspondent Wolfgang Behrends reports. 'That's what we learn during our visit to several facilities near Taipei. Upon closer examination, what looks, at first glance, to be completely incompatible is revealed to be a well-conceived model from which Europe could certainly learn.

Chang Gung Memorial Hospital, a 3,800-bed clinic near Taiwan's capital of Taipei, boasts one of the world's most modern proton therapy centres. Rapidly accelerated protons are applied here for precision radiation in cancer treatment. Professor Ji-Hong Hong, Vice-Superintendent, and Chien-Yi Yeh, Director of Technology, in the Radiation Oncology Centre, explain the principle: 'The protons are subjected to extreme acceleration in a cyclotron and directed at the tumour in the form of a bundled beam. Through the manner of energy discharge by the protons in the body, the tumour tissue is subjected to precise radiation, while the surrounding tissue is left untouched.'

The most frequent use of the procedure is to treat liver cancer, but also head and neck cancer, brain tumours, lung and breast cancers are treated with proton beams. Some 700 patients annually undergo proton therapy in the clinic. 'With many cancer patients it's not possible to fight the tumour with surgery or common x-ray radiation. In these cases, proton therapy offers the best chances.' However, this system is not only used as a last-ditch measure. 'Head and neck tumours have a notoriously high complication rate. The high precision of the proton therapy delivers these patients a better outcome because of fewer side effects and no collateral damage due to ionising radiation.'

Two different methods complement each other

After this impressive high-tech demonstration, the contrast in the neighbouring department could hardly have been greater. In the Traditional Chinese Medicine (TCM) Centre, everything revolves around acupuncture, pulse diagnosis and the qi energy network in the body. 'Our therapies are based upon wisdom from thousands of years and do substantially less damage to the body than many modern methods,' Director Dr Jiun-Liang Chen explained. However, the procedures have nothing in common with the widespread prejudices about esoteric medicine. TCM is a highly complex and precise discipline, as is readily visible in the department's apothecary, where more than 300 vegetable, animal or mineral ingredients are combined in individual powder mixtures according to precise criteria.

Photo: Behrends

Specialised TCM pharmacists compound unique drug mixtures from more than 300 ingredients.

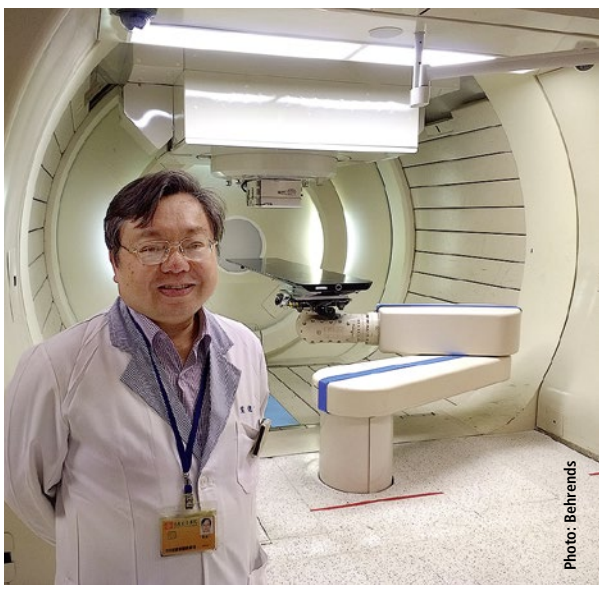


Photo: Behrends

Chien-Yi Yeh explains how proton therapy works: Protons are accelerated in a cyclotron and aimed precisely at the cancerous tissue. This procedure prevents radiation damage to surrounding tissues.

Even though high-tech radiation therapies and Traditional Chinese Medicine are worlds apart, their contradictory approaches complement one another very well, Chen believes: 'In our clinic, we have many cancer patients who undergo proton or chemo the-rapies and at the same time profit from TCM treatment, which helps against the strong side effects of the chemotherapy. We have had very good experience with the combination of these treatment approaches.'

Hospital and hotel in one resort

At the next stop we are surprised by another unusual combination. The Taipei Wellness Clinic and Resort in the Beitou district is equal parts practice community and wellness hotel. 'What we offer could be called a health vacation,' says Mark Chen, Executive Assistant to the Board and Administrative Department. Whilst the lower part of the building houses the medical facilities, the higher floors can scarcely be distinguished from a typical hotel. Both components are closely interwoven; menus and activities for hotel guests are tailor-made in accordance with the respective treatment plan.

The facility offers a wide range of treatments from one day check-ups, to medical and dietary advice, diagnostic imaging using MRT, CT and ultrasound, surgical, interventional and cosmetic treatments to fitness and wellness packages. The resort partners with clinics such as the Purple Sun Regenerative Medicine Centre, specialised in spinal and joint operations, and Universal Eye Centre Group, providing laser ophthalmology. The clinic offers a level of service that usually is only found in superior hotels: 'Even demanding interventions often involve no more effort than a visit to the dentist,' says Dr Wesley Chen, managing director of Purple Sun.

'Healthy life no longer means just the absence of sickness,' Mark Chen points out. That is why good food as well as visits to regional attractions are essential parts of the concept. The Taiwan government has also recognised the potential of such facilities for tourism and subsidises the hospital hotel. 'In the past years the significance of medical tourism has greatly increased,' he adds. 'We meet the challenges of this development with a holistic concept.'

Chien-Yi Yeh talks about the history of the Proton Centre, which took 20 years from initiation to opening

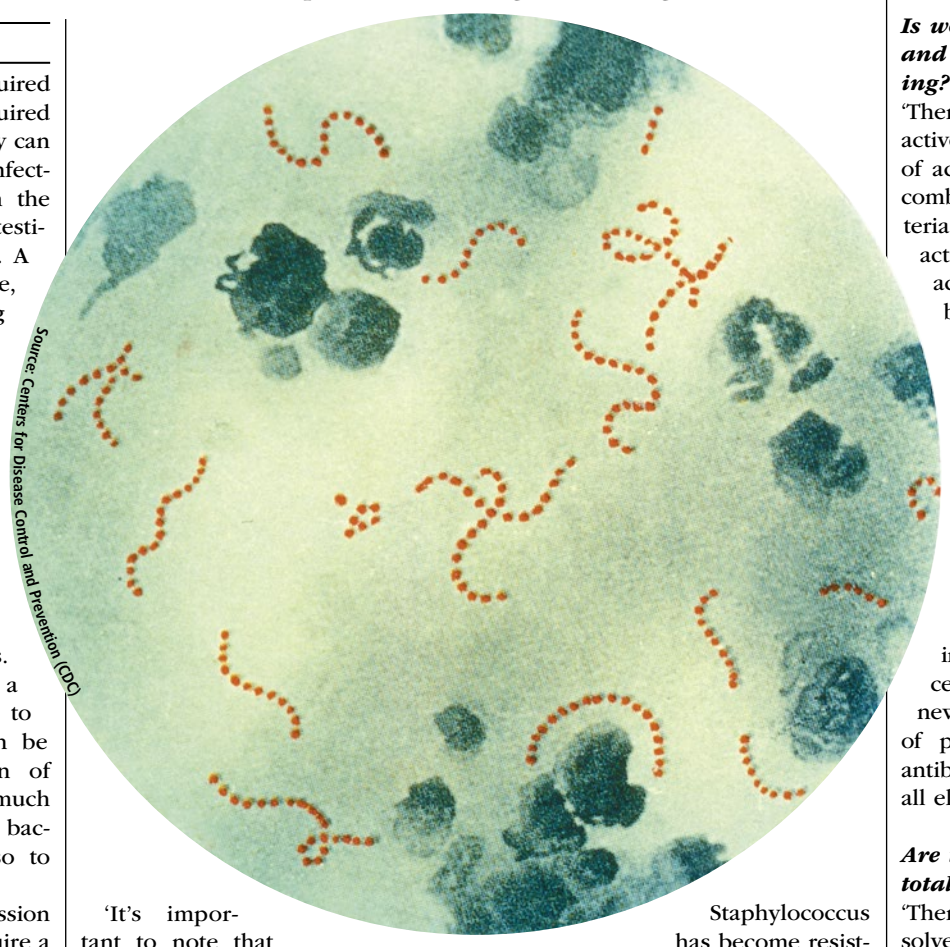
Calming lighting during MRI examinations is one of the measurements taken to ensure maximum patient comfort

An internationally coordinated strategy may help

HAIs are one problem – MDROs another

In view of the increase of multidrug-resistant organisms (MDRO), the World Health Organisation (WHO) has declared antibiotic resistance one of the biggest threats to global health. MDROs have become a major problem particularly in hospitals. Professor Dr Georg Häcker, President of the German Society of Hygiene and Microbiology (DGHM) and Director of the Institute for Microbiology and Hygiene at the University Hospital Freiburg, explains some strategies to prevent hospital-acquired infections (HAI), also known as nosocomial infections, and to contain the further development of multidrug-resistant organisms.

Interview: Sascha Keutel



Source: Centers for Disease Control and Prevention (CDC)

Dr Georg Häcker: 'Hospital-acquired infections are all infections acquired in or present in a hospital. They can be self-infections when the infecting organism is derived from the patient's own skin, gastrointestinal or upper respiratory flora. A severely ill patient, for example, treated in hospital over a long period of time, might inhale bacteria from his or her own oral microflora into the lungs and develop pneumonia. This is also considered a nosocomial infection – and is one that can hardly be prevented.

'HAIs, however, also can be transmitted from patient to patient, or from staff to patient, or they can be so-called environmental infections. Infections caused by sharing a toilet, or infections from staff to patient, to a large extent can be avoided. Complete prevention of all HAIs, however, is pretty much impossible since people and bacteria live at close quarters, so to speak.

'The many routes of transmission pose many challenges and require a wide variety of measures. In some cases it might make sense to remove certain bacteria from the patient, in order to prevent self-infection. Staff, visitors and fellow patients must be instructed to follow simple hygiene practices, such as hand hygiene. The patient environment, such as tables, or the toilet as well as instruments and equipment with patient contact must be disinfected or sterilised according to a scientifically validated plan.

'The patient microflora is most likely the biggest challenge because it can only be partially controlled and, obviously, cannot be removed. Implementation of effective hygiene measures in hospital routine, particularly in view of the often less than ideal working conditions, presents another problem.

'It's important to note that most HAIs are not caused by multidrug-resistant organisms. HAI and multidrug resistance are two distinct problems and the overlap of these problems – that is nosocomial infections caused by MDRO – is rather small.'

Are antibiotics still the only choice to fight infections?

'The short answer is an unconditional "yes"! While some bacteria have developed resistance against all active substances, this does not mean that all bacteria are, or will become, resistant to all antibiotics. Case in point: penicillin. Staphylococcus aureus and Streptococcus pyogenes used to be susceptible to penicillin; they had to develop resistance. Due to the medical use of penicillin, and related antibiotics, Staphylococcus has become resistant. Today, approximately 90 percent of Staphylococcus aureus in patient samples are penicillin-resistant. Streptococcus pyogenes, on the other hand, is still penicillin-susceptible.

'There are many different kinds of bacteria and they develop in very different ways with regard to resistance. As far as bacterial infections are concerned, antibiotics remain the first-line therapy and most bacterial infections can be successfully treated with antibiotics.

'Having said that – there were indeed cases of bacterial infections where no antibiotic was effective due to resistance. In Germany, these cases are very rare, but in some regions of the globe the situation is serious. Therefore, it's imperative that we try to contain the spreading of multidrug-resistant organism as much as possible. Most prognoses, for Germany and the entire world, see an increase in the number of infections that are difficult to treat or entirely untreatable.'

Is work to create new antibiotics and active substances progressing?

'There are indeed some enhanced active substances and combinations of active substances that effectively combat certain highly resistant bacteria. Additionally, there are new active substances, or classes of active substances, against certain bacteria. For some bacteria no substance has been developed.

'In general, this is a wide and complex issue. While it's true that the development of antibiotics does not enjoy top priority among the large pharmaceutical companies, there is some research activity. It's clear, though, that the one antibiotic that will effectively combat all bacteria is not in the wings. Bacteria will most certainly become resistant to the new antibiotics classes. Thus it's of paramount importance to use antibiotics correctly and strengthen all elements of infection medicine.'

Are there no advances regarding total antibiotics resistance?

'There is no single approach to solve the problem forever, but there are different approaches that help us to better understand the problem and evaluate the scope of the problem. Moreover, there are new ideas on how to strengthen healthcare structures to minimise the development and contain the spreading of antibiotics resistance. For some time, researchers have tried to use bacteriophages that infect and destroy bacteria that are resistant to antibiotics. This approach is promising but at this point it is too early to make any predictions regarding the possible success of such a treatment.'

What other strategies aim to stem the tide of MDROs?

'The term "multidrug-resistant bacteria" encompasses heterogeneous organisms and is also used inconsistently. One of these bacteria is MRSA, which causes different problems in different countries. In Germany, the number of MRSA infections has been decreasing for a few years. The most troublesome are the so-called gram-negative bacteria, another heterogeneous group, since antibiotics are basically ineffective with all infections they cause. In some countries these bacteria are ubiquitous; in Germany they are either imported or home-grown due to antibiotics use.

'Specific strategies tailored to different bacteria must be developed. Our most important "broad spectrum" strategy is strengthening and coordinating the three pillars of infection medicine: infections must be detected quickly and antibiotic susceptibility has must be determined quickly and reliably. This is the task of microbiology. Bacterial infections have to be treated quickly and correctly. This requires adequately trained physicians. Transmission of resistant bacteria between people, particularly in hospitals, must be avoided as much as possible – the task of hospital hygiene teams. The combination of these three strategies can reduce evolutionary pressure on bacteria and spreading of multidrug-resistant bacteria can be significantly contained.'

Should those strategies be applied on national/international levels?

'Each country has its own native healthcare system, which is very difficult to influence by international efforts. Also, the resistance situation differs from country to country. Thus, national strategies that consider local structures are pivotal. At the same time, knowledge transfer is important, since not all countries have adequate mechanisms in place to map and understand multidrug-resistant organisms. We all have to try to use the knowledge that exists on the global level.

'An internationally coordinated strategy would be helpful. Indeed, the key points have already been spelled out by WHO. But strategies that are successful globally not only need the political will but significant structural improvements and financial investments in the individual healthcare systems. Last, but not least, we need changes in lifestyles and our perception of the issue. We have to work on these strategies without falling prey to the illusion that they can be implemented quickly and that they will quickly yield major results on the global level.'

Professor Georg Häcker MD gained his doctorate in medicine in 1991, at the University of Ulm, Germany. Today, he presides over the German Society of Hygiene and Microbiology (DGHM) and is Director of the Institute for Microbiology and Hygiene at Freiburg University Hospital. In his research he focuses on the molecular mechanisms of cell death, cell death in the immune systems and the infection biology of Chlamydia trachomatis.

Nosocomial infections kill 15,000 patients annually in Germany

EU survey reveals worse countries

Hospital hygiene and how Germany compares in a European survey is somewhat divisive. Some believe Germany does well, whilst others emphasise the need to improve and for a stronger alignment with countries such as The Netherlands.

As hygiene specialist Professor Petra Gastmeier, at the Institute of Hygiene and Environmental Medicine in Charité University Medical Centre Berlin, pointed out: 'Compared to other EU countries, the prevalence of nosocomial infections in Germany is relatively low.' However, the expert concedes that Germany has a comparatively large number of hospital beds and hospital stays, so the disease burden is very high by EU comparison. Clearly speaking: The risk of contracting an infection increases with every visit to a German hospital. Based on current figures (Behnke et al.: Prevalence of nosocomial infections and use of antibiotics in German hospitals; DOI: 10.3238/artzebl.2017.0851), Gastmeier deems the German development positive: The number of hospital hygiene specialists has increased along with use of hand disinfection agents.

The figures Gastmeier presents still seem high: An annual 15,000 patients in Germany die from nosocomial infections, with 2,300 of these infections caused by resistant pathogens – a partially preventable cause, she believes. An important aspect arising from the study is the limit of the use of broad-spectrum antibiotics and a general awareness of resistance through antibiotic stewardship programmes.

How the fight against multi-resistant pathogens will progress still appears unclear, as the development of resistance has also been observed with the use of new, innovative antibiotics. Gastmeier is therefore advocating a more considerate, sensible use of antibiotics and emphasises that 30% of all prescriptions could be avoided.

Professor Petra Gastmeier heads the Institute of Hygiene and Environmental Medicine in Charité University Centre Berlin

Buy no product unless disinfection is detailed

Rigorous hygiene practices are vital

Nosocomial infections present enormous challenges for medical facilities, involving huge hygiene efforts from staff, on patients as well as medical and non-medical products. At MedtecLIVE 2019, in Nuremberg, Susanne Harpel (Dipl. Ing), Deputy Head of the Institute for Hygiene and Environmental Medicine at Giessen/Marburg University Hospital, presented desirable contamination efforts during the session 'Management of hygiene-critical surfaces in medical facilities'.

Routine surface disinfection and targeted disinfection are both necessary in hospitals, according to Susanne Harpel. Routine disinfection is ongoing, with all surfaces being disinfected – even when no detectable contamination is present. Targeted disinfection is carried out to eradicate contamination once it has occurred.

Whilst this may sound quite simple in theory, in reality the performance poses numerous challenges for those involved. 'If you imagine a basic bed area on a hospital ward, the surfaces appear relatively manageable. But, the reality is obviously very different because there are numerous surfaces patients touch,' Harpel pointed out.

A distinction is made between surfaces close to the patient, those further away, and those with particularly frequent hand and skin contact. The latter must be monitored particularly carefully to eliminate contamination and to reduce the infection risk they can pose. 'Everything the patient touches is colonised by microorganisms that are potential sources of infection. Numerous studies confirm that patients spread these microorganisms around a room.'

The design of bedrooms on wards challenges surface disinfection. 'Many hospitals want to offer patients rooms with a feel-good factor, or with a hotel character. Flooring with wood effect for instance is increasingly popular. However, there are huge differences in design which we have to deal with in daily routine,' Harpel underlines. The flooring often has very rough surfaces or gaps where dirt accumulates, therefore it is not suitable for thorough surface disinfection with mops or other cleaning equipment.

Cleaning medical devices also presents a significant problem for hospital hygiene. Legal requirements stipulate that manufacturers must provide users with detailed descriptions for equipment cleaning, for example of ultrasound scanners. 'If these instructions state that the ultrasound scanner should be cleaned with "a soft cloth, lukewarm water and mild detergent", this poses big problems because the control elements of an ultrasound scanner are in frequent hand and skin contact. A mild detergent therefore won't do; we actually need to use disinfection agents,' Harpel explains.

Source: Shutterstock/Photo-Art-Lortie

Requirements

These problems result in the following requirements:

Hygiene officers need clear information as to how a device, medical product or even hospital bedroom furnishings are to be disinfected, i.e. which disinfection agents and materials can be used and the concentrations and application times required.

It should be possible to clean all equipment with as few cleaning agents as possible, and monitors and various control elements should not require different solutions. This could also prevent agents being mixed up, or surface damage being caused due to a disinfection agent not being suitable for a specific surface.

As hospitals normally use wipe-down disinfection, surfaces should be designed and structured in a way that makes it possible to wipe them down, i.e. have as few corners, edges and grooves as possible. Surfaces should also be smooth and flush to ensure that no moisture can enter gaps and damage devices.

'When it comes to disinfection agents, we would really like an all-in-one solution,' Harpel explains. Material compatibility is important, and hand disinfection agents (especially those used by staff) must be kind to skin and mucous membranes. Agents should be widely effective despite short application times to ensure that (almost) all microorganisms are killed.

Harpel pleads for a greater say in procurement committees so that potential problems can be discussed prior to the acquisition of devices or materials. 'There must be a clear understanding how a product can be disinfected, and only when this is known should it be purchased,' Harpel concludes. (SKE)

Some surfaces are harder to disinfect than others

Just nebulise germs away

VALIDATION

Report: Brigitte Schenk

The Protestant Deaconess Hospital in Leipzig has used hydrogen peroxide nebulisation for several years. During the first test applications in 2015, I myself was still somewhat sceptical: Will it really be worth the effort? Can the associated process really be established without further ado in a hospital of basic and standard care? About two and a half years later, I can state with conviction: The introduction of the hydrogen peroxide nebulisation process as a supplement to the usual final disinfection was a complete success.

This was the case from the very first day, when a new intensive care unit was opened in September 2015 in Leipzig's Deaconess Hospital and a patient with a challenging spectrum of pathogens was admitted in the first few weeks. MRSA as well as 3MRGN Klebsiella pneumoniae and 4MRGN Acinetobacter baumannii were detectable at several smear sites, e.g. in the bronchial lavage. In this patient's treatment, I came across the hydrogen peroxide nebulisation process and management approved placement of a trial order.

Workflow for hydrogen peroxide nebulisation

In the preparation phase, disposable products are discarded and a final disinfection is carried out according to the disinfection plan. All surfaces must be dry and freely accessible; the mattresses must be tilted upwards and the drawers opened in the respective room. Subsequently, personnel from the technical staff tape the cover grids of supply and exhaust air so that the concentration remains constant during the exposure time. Smoke detectors are shielded with a special foam cover and additionally are temporarily switched off.

Now the possibility arises to position mobile ultrasound and X-ray devices, trolleys, etc. in the room, which have also been wiped with disinfectant, to have them de-contaminated as well. Furthermore, numerous monitors, infusion pumps, blood pressure cuffs and cables in the intensive care unit can also be exposed to the procedure without concern.

Trained employees now position the generator in a corner of the room, aligning the nozzle to the centre of the room. The volume controller is set on the basis of room volume and the measured humidity. To be able to verify the success of the nebulisation, five indicator sticks are laid out at different places in the room. After the device has been switched on, the employee has 30 seconds to leave the room. From the outside, the closed door is sealed with a gas-tight adhesive tape and marked with a sign.

The duration of the nebulisation depends on the room volume and may not exceed 30 minutes. This is followed by a 90-minute exposure time, after which a member of the cleaning staff opens the seal and, protected by a gas mask, enters the room to open the windows for a ventilation time of 45 minutes.

Is it worth all this effort?

The results and findings that we have been able to gather in the Deaconess Hospital so far are absolutely convincing. A significant germ reduction has been verified on various surfaces, especially in an outbreak situation.

The H2O2 nebulisation can also be used to reach areas that are difficult to access manually – bactericidal, fungicidal, virucidal and sporicidal. Even bacterial biofilms are affected, because the preparation used in our clinic is enriched with silver ions.

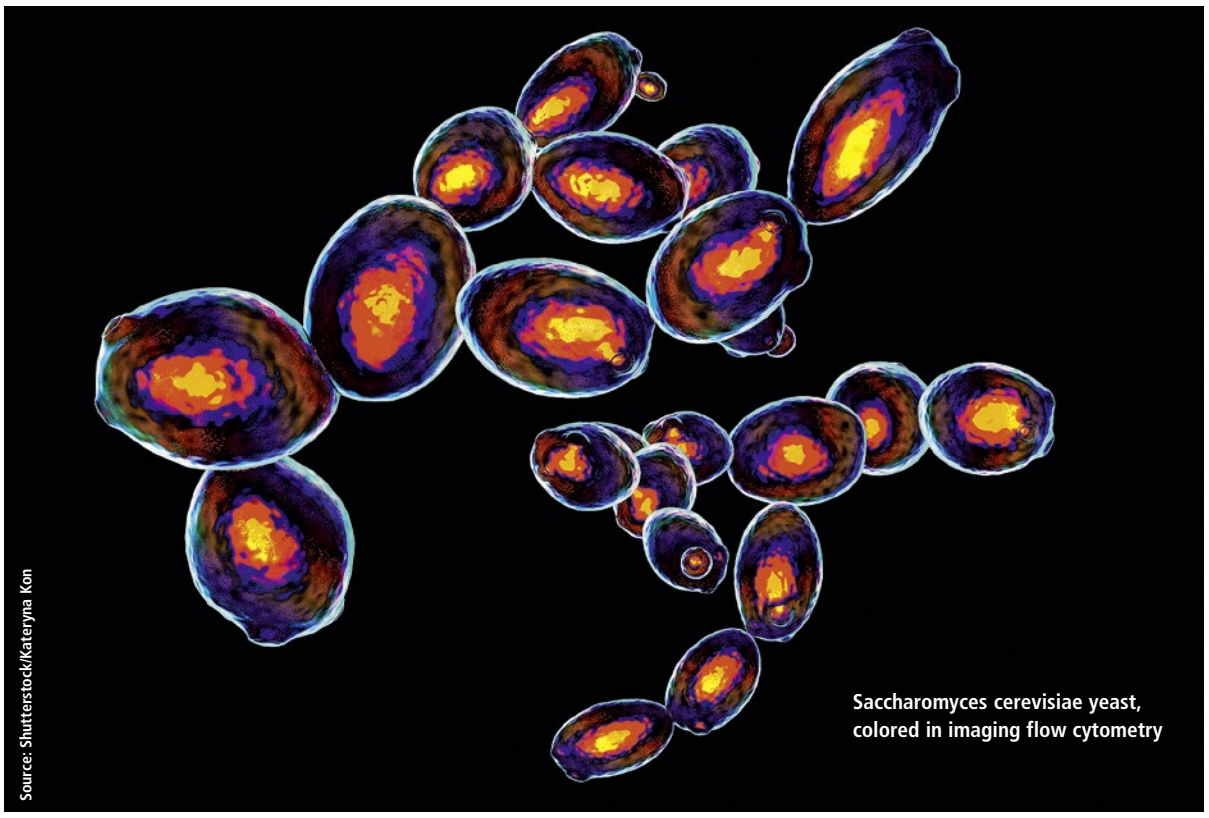
These enhance the effectiveness of hydro- gen peroxide, which results in dam-ages to the membranes of the micro-org- anisms. The compound is environmentally harmless – it breaks down into water and oxygen. When wiping disinfection is carried out manually, there remains a risk of in- sufficient application of aqueous solutions; however, this gap can be closed with a hydrogen peroxide nebulisation. Therefore, the pro-cedure is a valuable supplement.

The combination of wipe disinfection and hydrogen peroxide nebulisation has proved to be a real blessing from the very first difficult patient case to the present day.

Antibiotics: impact on microbiomes is a big concern

Sepsis needs early indication

The critical element in sepsis testing lies not so much in the location but in the timing and rapidity of results, according to Professor Jeannine T Holden from Beckman Coulter. Early identification enables treatment protocols to be delivered more quickly, offering better patient outcomes.



Source: Shutterstock/Kateryna Kon

Saccharomyces cerevisiae yeast, colored in imaging flow cytometry

Those most at risk, suggests Holden, are not patients in an intensive care unit – whose condition is already closely monitored – but individuals who arrive at the hospital emergency department after feeling unwell at home. She acknowledges flow cytometry to be potentially an effective tool for studying the immune system and identifying sepsis, but it requires time to perform the test and specific expertise and resources to deliver it.

What is essential, according to Holden – who is chief medical officer of Beckman Coulter Diagnostics and of Beckman Coulter Life Sciences (both part of the Danaher Corporation) – is to have a sepsis test that can be performed routinely on emergency department patients as part of the standard blood test analysis, and deliver results promptly.

Data shows that mortality from severe sepsis and septic shock is decreased by 7.6% per hour by the early and appropriate administration of antibiotics, while early identification and treatment of sepsis can also reduce the cost of sepsis-related care. Yet diagnosing sepsis, often in the emergency department, remains a challenge.

Holden outlined how the Early Sepsis Indicator from Beckman Coulter, together with other laboratory findings and clinical information, can provide clinicians with an alert as to the possibility of sepsis, or risk of developing sepsis. The Early Sepsis Indicator is part of routine blood work, reported as part of a complete blood count with white blood cell differential, so there is no additional test to order or analysis effort required.

With a background as a haematopathologist, teaching medical students and residents as a professor at Emory University in Atlanta, as well as diagnosing patients with leukaemia and lymphoma, Holden has been with Danaher for six years. 'Sepsis is immune dysregulation,' she explained. 'The underlying trigger is typically infection, but sepsis is not the infection itself – it's the body's reaction to infection; the fact that the body is over-reacting to infection and, because it's over-reacting, the immune response is so vigorous that it can damage organs. Sepsis is not contagious – there is no quarantine – but if you have a bacterial infection it is the body's job to elicit an appropriate immune response to control it. If you do not have a sufficiently vigorous response, you will die of the infection. But, if it's too vigorous, you will have sepsis.'

Flow cytometry, continued Holden, is a good tool for studying the immune system and Beckman Coulter has products in that sphere specifically designed to interrogate the normal immune state and deviations from the normal immune system. 'Flow cytometry is not just phenotyping; you can pull a subset of cells out and study them; there is a lot of flexibility there, but it's currently not readily available 24/7,' she added. 'What you want is a test that is available straight away and does not require an expert to perform. The question of timeliness is important.' This is why the Early Sepsis Indicator is proving a pivotal tool; it is part of routine haematology testing and the result is rapid.

Beckman Coulter also offers the Procalcitonin (PCT) assay, intended for the quantitative determination of PCT in human serum, EDTA or lithium heparin plasma, for identifying sepsis. 'We have just received the CE mark for a new immunoassay for procalcitonin that has excellent precision of the assay at low levels and helps distinguish patients who are at risk of sepsis. It is another biomarker, another piece of information.' It is more expensive and takes more time compared to the rapid Early Sepsis Indicator – which is not expensive as it is on the haematology analyser and not a separate assay – but the PCT assay provides doctors with an additional marker when they are already suspicious of sepsis.

Holden also spoke of the dangers of antibiotic over-use, particularly in the food industry, and the trend for people to change their eating habits, often adopting a vegetarian or even vegan diet. Within that area, she highlighted the growing recognition of the significance of the microbiome – the minute creatures that live within and on the human body – and the need to encourage and nurture them. 'The question of antimicrobial stewardship and antibiotic resistance are closely related,' she said. 'For me, a big concern is the use of them in industry and the overall impact on our microbiomes, because one of the defences we have against infection is the microbiome, so if we alter the microbiome we may lose that defence. The gut microbiome is very important and what you eat affects your microbiome.' She believes greater understanding of the immune system and the microbiome will play an increasingly critical role in medicine in the next few years.

Safety products reduce the risk

Abolish needlestick injuries

If a health sector employee falls ill with a bloodborne disease, the cause is often a previous injury from a sharp, contaminated object. Direct blood-to-blood contact, such as with a needlestick injury (NSI), is among the recurring causes of infection. It isn't possible to vaccinate against HIV, for instance, and the consequences of an infection remain fatal.

Among the most effective ways to protect medical staff from needlestick injuries (NSI) is to use safety products. The specialist manufacturer Greiner Bio-One presents a portfolio of products to prevent such accidents.

Healthcare employees handle a wide range of tasks and are exposed to many risks. When working with sharp and/or pointed objects, such as cannulas, the risk of injury and infection with transmissible pathogens increases when handling and disposing of these products.

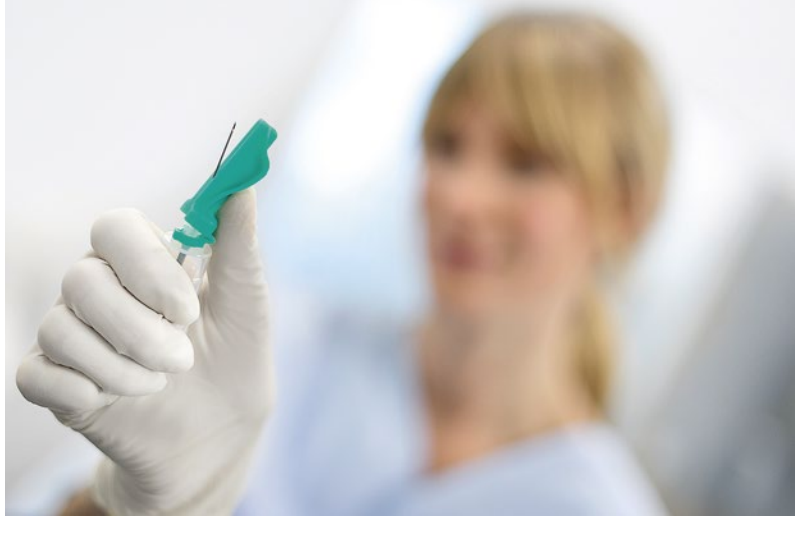
'Unfortunately,' observes Greiner Bio-One, 'potential hazards are often not noticed or taken seriously and those affected attribute too little – or sometimes even no significance – to their injury caused by a contaminated needle.'

A needlestick injury can be due to a mechanical failure of the safety mechanism, or incomplete activation or improper use by the user, the company points out. 'However, there are varying degrees of technical development of the safety products to avoid these kinds of malfunctions.[1] It's particularly important that correct handling is practised and always to be careful when dealing with contaminated objects.' The company reports that its safety products are engineered to provide the best possible protection from bloodborne diseases caused by NSI, including:

- VACUETTE safety blood collection sets: A safety mechanism is activated after blood has been collected and the needle is still in the vein, thus protecting against needlestick injuries.
- The Vacuette Clix safety hypodermic needle, which has a built-in safety shield that irreversibly encloses the needle after it is activated. Successful activation is indicated by a clearly audible 'click'.
- The Vacuette Quickshield safety tube holder, equipped with a mechanism to keep the needle safe after venipuncture and thus protect against needlestick injuries. 'In addition to their high degree of safety, the products distinguish themselves with their optimised ergonomic design,' the manufacturer adds.

Details: www.power4safety.com.

1 Tosini, W, et al. 2010. Needlestick injury rates according to different safety-engineered devices etc. Infection Control and Hospital Epidemiology, Vol 3 No.4.



'I think we are going to find out that the immune system is important for things we did not previously think about – for dementia, for example. 'I think, as we get a better understanding – in the same way we are having this revolution in cancer, based on the immune system and manipulating the immune system to treat cancer – we are going to be able to do that with a lot more diseases by understanding the way the immune system is driving the underlying pathophysiology.

'Generally speaking, I think drivers we will see will include immunology in general and specifically regarding diseases we do not currently think of being driven by our immune system. Our interaction with the microbiome will continue to be important and we will have an increasing understanding of its impact.'

Within that emerging therapeutic trend, Holden sees industry evolving products to meet that changing landscape.

Source: Shutterstock/Sirirat

Escherichia coli colonies: medical technicians working on bacterial culture and drug resistance of pathogens in the laboratory

CORRECTION

The liquid chromatography/mass spectrometry article in EH-2-2019: The author of this in-depth report is Debadeep Bhattacharyya PhD, Senior Marketing Manager at Thermo Fisher Scientific.

It was not supplied by the life science marketing agency BioStrata, as the introduction may have implied.

Jeannine T Holden MD MBA is vice-president of medical and scientific affairs and chief medical officer for Beckman Coulter Diagnostics, where she is responsible for the medical oversight of Beckman Coulter. Prior to joining the organisation in 2013, she was associate professor and director of haematopathology and flow cytometry at Emory University School of Medicine in Atlanta, Georgia. During that tenure Holden built and managed the haematopathology reference laboratory, providing an expert consultation service in microscopy, flow cytometric immunophenotyping, fluorescence in situ hybridisation, cytogenetics and molecular diagnostics.

New rapid test for sepsis

Researchers at the University of Strathclyde have developed a low cost test for earlier diagnosis of sepsis which could save thousands of lives. The simple system for sensitive real-time measurement of the life threatening condition is much quicker than existing hospital tests, which can take up to 72 hours to process. Using a microelectrode, a biosensor device is used to detect if one of the protein biomarkers of sepsis – interleukin-6 – is present in the bloodstream. The results of the research project show that increased levels of the molecule can be detected by the test as quickly as two and a half minutes.

The small size of the devices – microelectrodes on a needle shaped substrates – makes them ideal for initial testing and also continuous monitoring for sepsis, which is notoriously difficult to diagnose. The device takes a pin prick of blood which is then put on the chip for the result to be read. Its needle shape means it can also be implanted and used on patients in intensive care. The UK Sepsis Trust estimates that around 52,000 people in the UK die every year and six million globally from the condition, yet with early diagnosis and the correct treatment, most people make a full recovery.

Algorithms need development to assist routine pathology

Seeking the right questions

Report: Mark Nicholls

Artificial Intelligence (AI) is destined for a significant role in assessing histology data but the key to developing the necessary algorithms lies in data quality – rather than the quantity, according to Professor Jens Rittscher. He also warns that we are some distance from seeing AI replacing human pathologists in this scenario, primarily because presently the risks of automated decision-making are not understood. The core to developing the necessary algorithms to drive AI to support better data assessment, he said, is the availability of annotated data for training, validation, and testing.

Rittscher, Professor of Engineering Science at the University of Oxford, explained that certain efforts focus on collecting a very large number of cases to develop algorithms to assist routine pathology. However, we should not underestimate the importance of 'highly-curated data' that are being collected and annotated with a specific clinical question in mind.

'It's the precision of the question you ask and then the quality and depth of the data,' he said. 'As we develop predictive models, I think it will be necessary to set up better prospective cohorts to validate these methods going forward, because there is only so much you can learn from retrospective data.'

Source: Shutterstock/anyaivanova

He pointed to three key ways that AI will assist histology data assessment: workflow improvements; helping to build a bridge between molecular tests and clinical practice, and applying new imaging approaches.

'With workflow improvements, if we can predict what other molecular tests should be run on a specific case or, in the case of referral to a specialised centre, which histopathology would be helpful to assess the risk profile, then automated reporting is going to be important.' This will be of particular relevance when a specialist is not available, when time is of the essence, or there is a need to order more complicated tests.

Today, it is difficult for oncologists to extract information from a pathology report. Including a visual summary of certain key histological features would dramatically improve the accessibility of the pathology report and help to close the gap between the two disciplines, he said.

Rittscher's team recently conducted new research showing molecular subtypes of colorectal cancer can be predicted using histology alone. 'This is one of the prototypical examples where you can now add information that pathologists could not really provide before,' he said.

A third area is the application of new imaging methods to pathology images and looking at multiple protein markers in the same tissue section. 'This is where the human will be overwhelmed by the information and need guidance by a computer,' he continued. 'Broadly, it will look at computer assisted forms of diagnostics for pathologists and this, I think, could dramatically enhance the role of pathologists

AI will complement pathologists' input

However, Rittscher is adamant that such technology will not replace human input, but will complement it. 'I think the potential that AI can replace human pathologists is overblown and partially unfounded because we do not really understand the risk of automated decision-making, such as whether a patient will accept it, or liability issues,' he said. 'But where AI is good is in providing quantitative information and adding a quantitative aspect to pathology that humans cannot assess reliably today.

'I think that is essentially what will drive the evolution of pathology and the convergence of further technologies in pathology – digitisation of slides, the quantitative information and the wider visibility of in vitro diagnostics – holds the potential to change how the different clinical disciplines work together today and give pathologists a completely new role.'

'However, he added, 'This also has broad implications for the education and training of pathologists, he added.

A 'bottleneck' in any advances remains because of the limited availability of experts, particularly in terms of the time needed to curate and annotate large data sets. 'It's a labour-intensive task to curate these and annotate them to the quality and specificity that you can actually use them later on,' he pointed out.

To optimise experts' time, computer assisted tools need to be developed that effectively support the generation of validated image level annotations.

He believes the future will see a strengthening in the capability of pathology departments to find and deliver better routes into molecular or in vitro tests and to make the data in the pathology report more accessible to other clinical disciplines, such as referring physicians or oncologists.

Jens Rittscher is Professor of Engineering Science at the University of Oxford, an appointment held between the Institute of Biomedical Engineering and the Nuffield Department of Medicine. He is a group leader at the Big Data Institute and affiliated to the Ludwig Institute of Cancer Research. Previously, he was a senior research scientist and manager at GE Global Research in America. His research focus is on enabling biomedical imaging via the development of new algorithms and novel computational platforms, with a current focus to improve mechanistic understanding of cancer and patient care through quantitative analysis of image data.

Living cells are the essential biomarker

Personalisation is a distant vision

Therapies tailored to suit an individual patient are high on the wish list of medical researchers. To accelerate development towards personalised medicine, a team in Munich, Germany, is focusing on innovative diagnostic tools. 'At this point, however,' concedes Professor Oliver Hayden, Heinz Nixdorf Chair of Biomedical Electronics at Munich's Technical University, 'personalisation is still a rather distant vision.' Diagnostic tools that provide quantitative data are needed to make that dream a reality.

Thus, Professor Hayden and team are not engaged in conventional medical electronics research. They explore new forms of flow cytometry to analyse cell function. 'The living cell is the essential biomarker,' Hayden emphasises. He is convinced that currently used biomarkers, such as blood values and inflammation markers, do not offer sufficient information for personalised therapies: 'It's not the individual protein or the individual gene that is the smallest functional unit of the organism.'

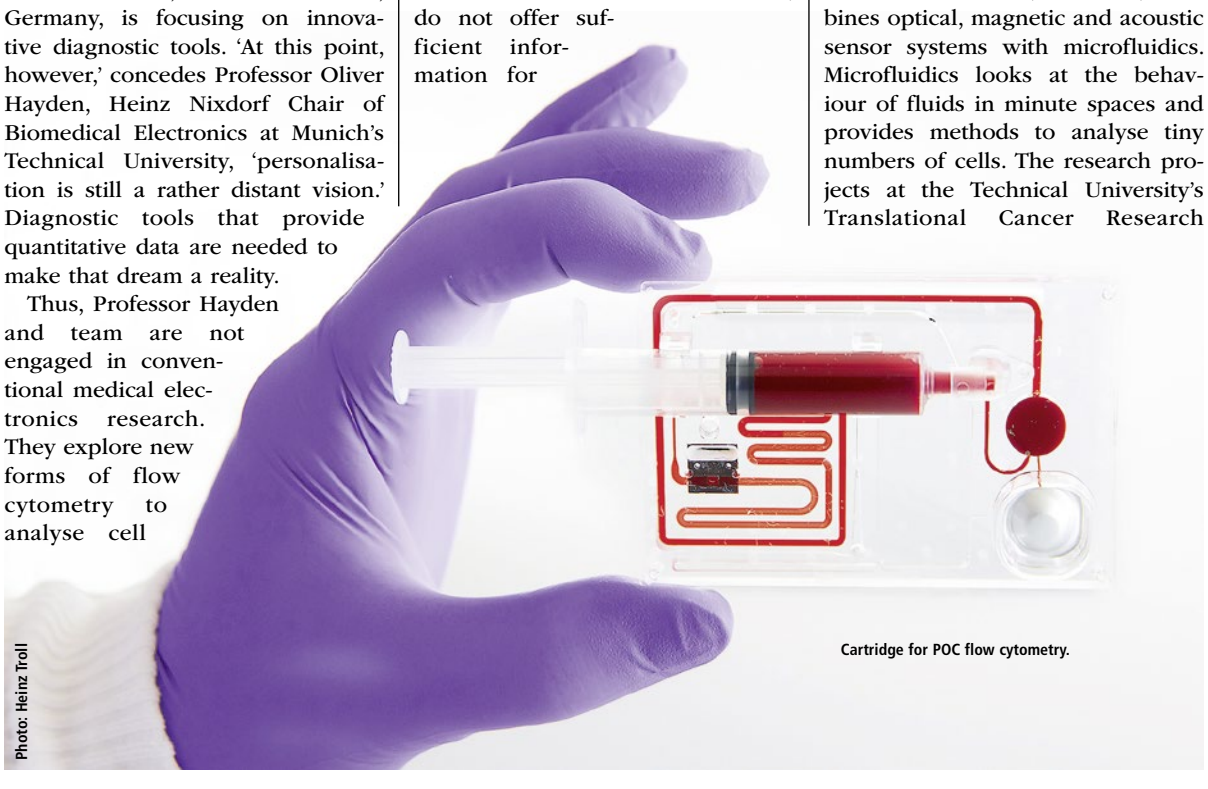


Photo: Heinz Troll

Cartridge for POC flow cytometry.

The Munich team, therefore, combines optical, magnetic and acoustic sensor systems with microfluidics. Microfluidics looks at the behaviour of fluids in minute spaces and provides methods to analyse tiny numbers of cells. The research projects at the Technical University's Translational Cancer Research Centre (TranslaTUM) focuses on the cooperation of an interdisciplinary team of engineers and clinical researchers to develop new diagnostic methods.

'Potentially our technologies can be used at the point of care, the central lab or in pre-clinical research,' says Hayden, who by the way cannot understand the current hype about POCT. 'The central lab will never be obsolete,' he emphasises. If a biomarker is stable enough to be transported and the relevant parameter does not have to be determined right away, POCT in Hayden's opinion does not make much sense in a clinical environment – not to mention the cost factor. 'The central lab is and will remain the most cost-efficient solution,' he says.

'Laboratory medicine is in fact an industrial process; you try to standardise, achieve maximum throughput and keep the costs down. Thus it's important, as in manufacturing, to integrate pre-analytics, analytics and post-analytics in a single workflow, which indeed his team aims to do. 'Workflow integration is often seen as relevant only to industry. But any university that wants to be competitive has to work on integrative solutions,' Hayden underlines, adding 'their mandate is translation; that is, at some point, the team's lab developments have to arrive at the bedside or in research.' The research centre TranslaTUM, at Munich's hospital rechts der Isar campus, Professor Hayden says, 'will enable engineers to speed up research and, through cooperation with clinicians and companies, to fulfil its translation mandate.'

Professor Oliver Hayden is Heinz Nixdorf Chair of Biomedical Electronics at the Technical University of Munich. Born in Austria, in 1999 he gained a PhD in biochemistry in Vienna, and then undertook postdoctoral research in nanotechnology at Harvard. In 2011 Hayden also received an MBA from Julius Maximilian University in Würzburg, Germany. The scientist's work has gained numerous awards, e.g. in 2017 the European Inventor Award for developing a rapid blood test for malaria. He has authored more than 80 publications and is a named inventor or co-inventor of around 80 patent families.

Improving patient outcomes with rapid, reliable microbe identification

The Bologna Workflow System

Authors: Miriam Cordovana and Dr Markus Meyer

Many countries across the world are challenged with a rising number of incidences of multi-drug resistant (MDR) organisms infecting the population, and for several years, a clear pattern of increased resistance has emerged in southern and eastern European countries. For example, in countries such as Italy, a reduced number of therapeutic options remain available for highly pathogenic infections, so research is targeting technologies that can rapidly detect infecting organisms with a high degree of accuracy, and establish the level of antimicrobial susceptibility.

A global health threat

Gram-negative bacteria are the most common cause of sepsis – a highly prevalent and deadly infection occurring worldwide – followed by Gram-positive bacteria and fungi. Fast isolation and species identification is therefore critical to provide a targeted therapeutic strategy and de-escalate from broad spectrum antibiotics as soon as possible. Sepsis is thought to impact approximately 27-30 million people globally every year, with one third dying from the condition, so fast identification methods are required that allow clinicians to rapidly act upon results and manage blood stream infections.

Carbapenems are the most important family of last-line antibiotics for treating MDR Gram-negative bacterial infections, and carbapenem-resistant *Enterobacteriaceae* (CRE) have emerged relatively recently as a class of bacteria that are not susceptible to carbapenem treatment. Isolates that produce carbapenem-hydrolysing β -lactamases (carbapenemases) are the key target for studies to determine resistance mechanisms of CRE. Italy has one of the highest instances of carbapenem-resistant *Klebsiella pneumonia* in Europe, with 33.5% of invasive isolates showing resistance. The *Klebsiella pneumoniae* Carbapenemase (KPC)-producing *K. pneumoniae* family is endemic in Italy and represents a severe public health concern, making rapid detection of these isolates a top priority.

Until recently, techniques including the modified Hodge test, disk-diffusion synergy test with inhibitors, and Carba NP (Nordmann Poirel) test, have either been slow (up to 24 hours) and time-consuming, lacking sensitivity, or have a limited number of targets included. Now, matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF MS) technology is recognised as a reliable, reproducible method to identify bacteria from positive blood cultures, and rapidly detect carbapenemase-producing bacterial strains.

Revolutionising the workflow

The hydrolytic activity of bacterial carbapenemases can now be detected by sensitive functional assays, based on the distinct mass changes of the carbapenem molecule after enzymatic cleavage. In contrast to previous methods, this MS-based phenotypic assay – Bruker's MALDI Biotyper Selective Testing of Antibiotic Resistance-β-lactamase (MBT STAR-BL) – can be applied directly from positive blood cultures, after MBT Sepsityper isolation.

The S. Orsola-Malpighi University Hospital in Bologna, Italy, recently introduced the integrated *Bologna Workflow* to the Bacteriology, Mycology and Mycobacteriology section of the hospital's Operative Unit of Microbiology, for rapid and cost-effective microbial identification and antimicrobial susceptibility testing (AST) from positive blood cultures. This is an urgent priority in clinical microbiology, as the spread of resistance against third-generation cephalosporins and carbapenems among Gram-negative bacteria poses a high burden on the Italian healthcare system, and is rapidly rising elsewhere in Europe and overall worldwide.

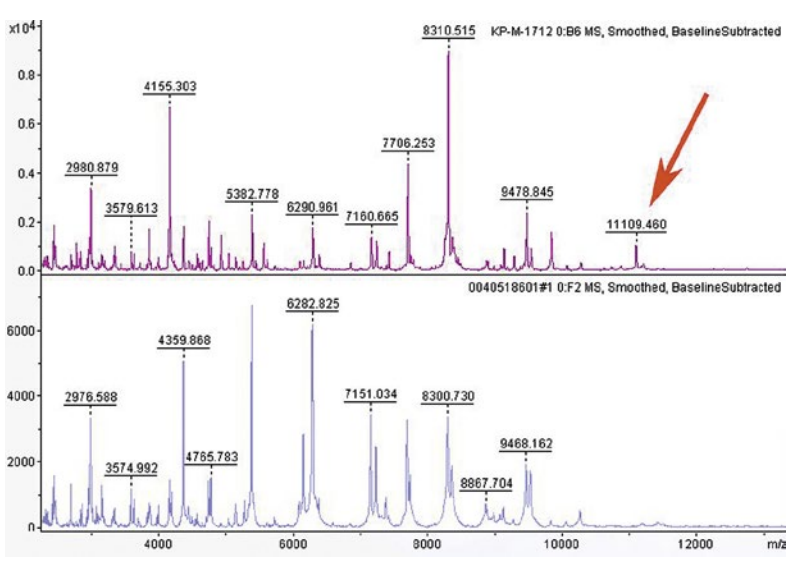


Figure 1: The pKpQIL plasmid-related peak in the MALDI mass spectra of K. pneumoniae. The upper spectrum shows a KPC-producing strain exhibiting the specific 11,109 m/z peak (red arrow). The lower spectrum shows a negative control, without the specific peak. Reproduced from reference in accordance with the Creative Commons License (https://creativecommons.org/licenses/by/4.0/).

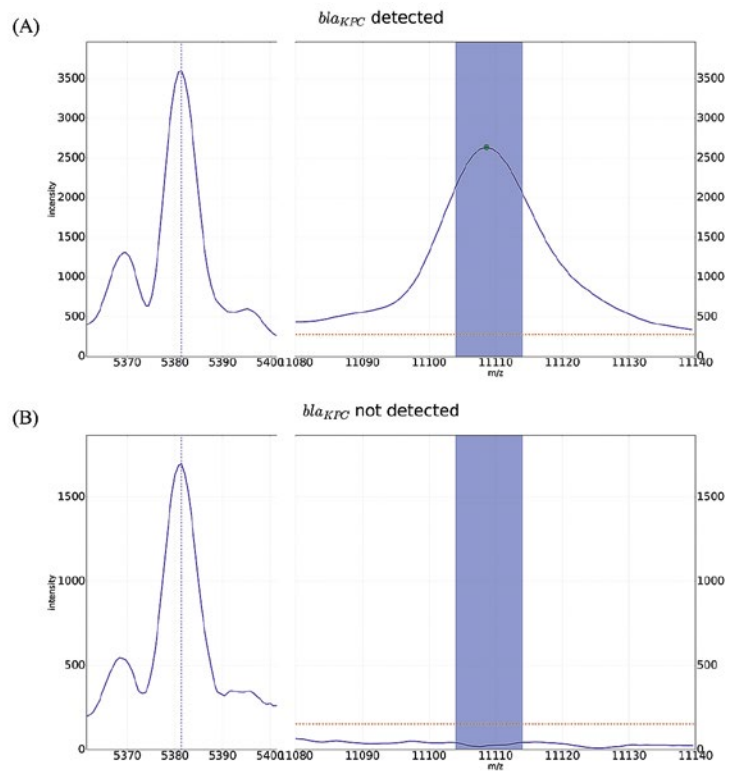


Figure 2: Detection in the window of m/z 11,109 +/-5. The dotted red line corresponds to a multiple of the average noise in the spectrum. It is used as a threshold for the intensity in peak detection. (A) KPC-positive K. pneumoniae strain with peak for the pKpQIL plasmid. (B) KPC-negative strain. In the detection window only noise below the detection threshold can be observed. Reproduced from reference in accordance with the Creative Commons License (https://creativecommons.org/licenses/by/4.0/).

Detecting resistant microbes

KPC-producing *K. pneumoniae* first emerged in Italy in 2010 and since then, the Bologna hospital laboratory has been conducting a research project to phenotypically characterise and store the strains, and evaluate different methods of detection. Lau et al. (2014) discovered a specific MALDI-TOF mass peak at 11,109 m/z appearing in KPC-producing isolates, which is related to the pKpQIL plasmid carrying the bla_{KPC} gene.

The automated identification of these KPC-producers, by detecting this specific KPC-related peak in the MALDI-TOF MS spectra, is now implemented in the MBT Subtyping Module, allowing a "presumptive KPC" result (Figure 1 and Figure 2). This innovative approach was applied first to bacterial plate cultures, then directly to positive blood culture bottles, using the bacterial pellet obtained using the MBT Sepsityper, which enabled reliable and rapid identification of KPC-producing *K. pneumoniae* strains. The automated peak detection allowed for 100% specificity and 85.1% sensitivity. In addition to the subtyping, the STAR-Carba test for confirmation of carbapenemase production showed 100% specificity and sensitivity.

The Bologna group is achieving a turnaround time for detection of KPC-producing isolates of 10 min to 1.5 hours, and showed that this novel MALDI-based approach uniquely provides real time detection of an antibiotic resistance marker, simultaneously with species identification.

Resistance detection in the future

By incorporating the MALDI MS-based approach the laboratory at the S. Orsola-Malpighi University Hospital can perceive early warnings for KPC-producing strains, facilitating the rapid initiation or change of therapeutic action and future infection control measures.

The future will see a wide scope for the extension of KPC-subtyping, as well as for the addition of new resistance markers and resistance detection methods. There is an increasing need for more 'customised' susceptibility testing, tailored by the results of species identification, combined with the epidemiological data of each setting. The ever-increasing spread of uncommon opportunistic pathogens and the growing proportion of immunocompromised patients for specific pathologies or medical treatments, is of significant concern. In the future this could present a further challenge to AST. Consequently, the faster microbiologists can identify the organisms, the stronger the overall patient outcomes will be.

S. Orsola-Malpighi University Hospital

More than 400 years ago the Bologna University Hospital Authority St. Orsola-Malpighi Polyclinic became the first hospital in Bologna. Today it is home to the School of Medicine and Surgery. The Polyclinic, an internationally acclaimed institution for the study and treatment of pathologies, organises annual medical conferences and conventions attended by professionals of international fame. The hospital develops and delivers multi-specialist research, education and training in an integrative manner, and promotes innovation and pursues the highest degree of patient/customer care and the training of medical students, as well as expanding the full potential of its skilled staff through goal sharing and assuming responsibility for any results. (https://www.aosp.bo.it/content/home).

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Miriam Cordovana is a Biomedical Laboratory Technician at the S. Orsola-Malpighi University Hospital, which she joined in May 2007, following roles at the University Hospital of Florence Careggi and the Human Genetic Laboratory of the University of Florence. Miriam oversees the processing of biological samples, from their arrival at the laboratory, through identification to the execution of antimicrobial susceptibility testing. She has played an integral role in the department's aim to optimise the entire workflow for blood culture microbial testing.

Dr Markus Meyer is a Global Product Manager at Bruker Daltonics. He gained his PhD in cell biology, biochemistry and microbiology at the University of Münster, Germany, and joined Bruker in 2005 as an Application Specialist in Clinical Proteomics.

Bioanalytical promise: Surface-enhanced Raman spectroscopy

The lab-on-a-chip SERS platform

Analytically sensitive and specific detection of pharmaceuticals or metabolites in bodily fluids, as well as fast and reliable detection of human pathogens, are major challenges for instrument-based analytics in medical diagnostics.

Over the past few years the combination of *surface-enhanced Raman spectroscopy* (SERS) and microfluidic devices (*Lab-on-a-Chip*) has emerged as a perfectly suited technology to ensure an automated and reproducible measuring environment and/or to analyse nanolitre volumes. The key feature of SERS is its ability to detect with molecular-specificity minute concentrations of pharmaceutical substances.

The required sensitivity is achieved by using plasmonic active metallic nanostructures, such as colloidal silver or gold nanoparticles, or nano-structured or micro-structured metallic surfaces. Furthermore, this method can be applied directly, i.e. without complex sample purification protocols, to detect individual pharmaceutical agents or metabolites in complex human matrices, such as urine, plasma or sputum, in concentrations of few mg/mL and even below µg/mL.

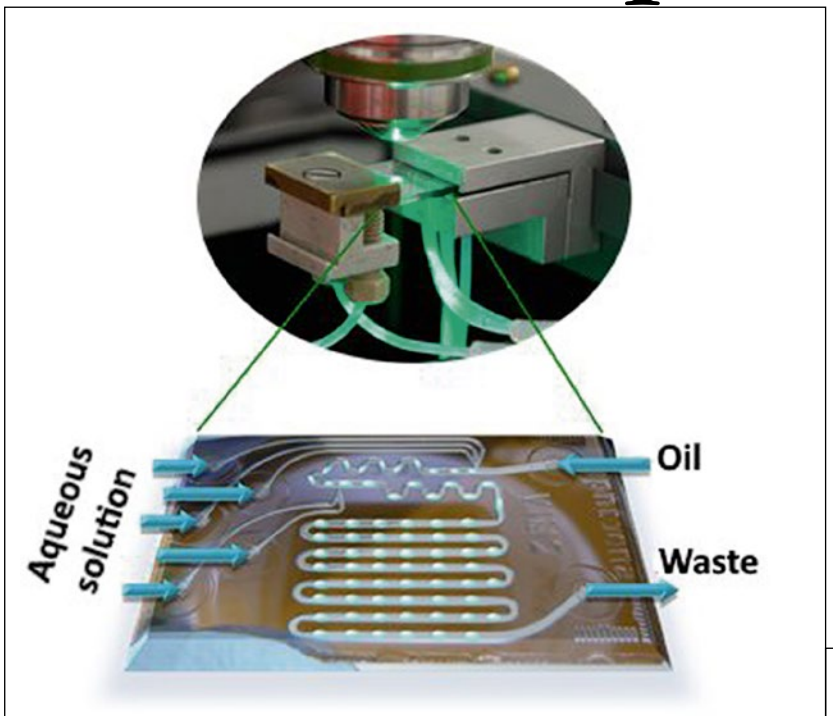


Figure 1: *Lab-on-a-Chip* SERS platform developed at Leibniz-IPHT Jena. Above: Photo of the lab setup. Below: Illustration of the microfluidics chips with aqueous droplets in the oil flow.

While SERS offers enormous potential in bioanalytics, it is not yet part of the routine diagnostic workup. This might to some extent be due to the high quality requirements with regard to SERS-active nanostructures which have to ensure reproducible signal intensity. Microfluidic devices, i.e. *Lab-on-a-Chip* can overcome the drawbacks of SERS such as the hard-to-control aggregation of the colloidal metal nanoparticles.

Currently, there are two types of *Lab-on-a-Chip* SERS platforms: flow-through or continuous flow platforms and segmented or droplet-based platforms. In flow-through platforms either metallic colloidal nanoparticles are mixed with the samples to be analysed, or stationary metallic nanostructures are integrated in the channel system. This approach avoids the evaporation of liquids, which occurs during conventional SERS measurements on open platforms. A disadvantage, however, is that sample liquids permanently wet the channel walls, which may result in the so-called *memory* effect (Memory effect describes a situation when the molecules of the sample get enriched over time on the surface of the channels. This may result in an overestimation of the detection limits).

On a segmented flow platform, particularly droplet-based SERS (Figure 1), cross-contamination can be fully avoided, since aqueous droplets are transported in an oily matrix. Thus there is no contact between the sample, resp. the metallic colloids and the channel walls. Furthermore, each droplet can be considered a micro-cuvette or a micro-reactor. Thus many spectra can be fed quickly and in an automated way into a database.

The authors' working group successfully used the droplet-based *Lab-on-a-Chip* SERS technology to detect pharmaceuticals and metabolites in bodily fluids and to identify mycobacteria. In these studies human urine was spiked with the antibiotic levofloxacin. Concentrations between 0.45 mM (162.6 µg/mL) and 1.8 mM (650.5 µg/mL) were detected. According to relevant literature the expected levofloxacin concentrations in urine are 1.38 mM ± 0.68 mM and a measured minimum concentration of 0.45 mM 4 hours post administration of 500 mg. Furthermore, the standard addition method was successfully used to detect nitroxoline (NTX) in human urine. Figure 2A shows a typical SERS spectrum of NTX and the concentration-dependent evolution of Raman-intensity of a marker band. The results presented above show that *Lab-on-a-Chip* SERS is a promising bioanalytical tool for urine analysis.

Moreover, enzyme activity of thiopurine methyltransferase (TPMT) in lysed erythrocytes was successfully determined. This involved tracking the transformation of the drug 6-mercaptopurine into 6-methylmercaptopurine, which in turn allowed conclusions regarding TPMT activity. No and normal TPMT activity were distinguished with 96% accuracy.

As far as the detection of pathogenic bacteria is concerned, the *Pseudomonas aeruginosa*-specific metabolite pyocyanine can be quantified with SERS. Using a robust SERS substrate pyocyanine was detected in artificial sputum depending on the concentration in the relevant area in cystic fibrosis patients who frequently show Pseudomonas aeruginosa colonisation.

Finally, *Lab-on-a-Chip* SERS was successfully used to identify mycobacteria in order to facilitate physicians' decision-making regarding medication. Figure 2B shows the chemometric model for the identification of bacteria.

To summarise: *Lab-on-a-Chip* SERS technology has high potential for clinical applications. Further studies with clinical samples are required to confirm these initial findings.

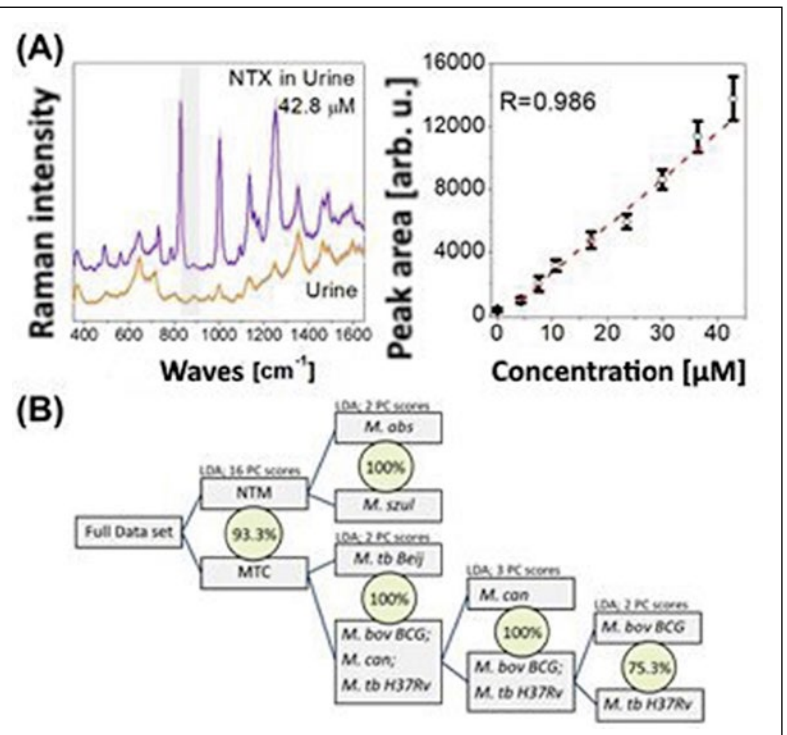


Figure 2: (A) The SERS spectrum of NTX in human urine and the background-SERS spectrum of pure human urine (measured with the *Lab-on-a-Chip* SERS setup). Linear dependency of the measurement signal (peak area of the marked Raman-band) and the concentration of an NTX-spiked urine sample. (B) Identification of mycobacteria: structure and parameter of the identification tree of the chemometric model based on the database that was created.

Dr Dana Cialla-May[1,2,3]

Dr Izabella J Jahn[1,2,3]

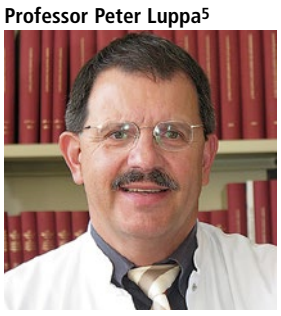
Dr Anna Mühlig[1,4]

Olga Žukovskaja[1,2,3]

Dr Thomas Henkel[1]

Dr Karina Weber[1,2,3]

Professor Peter Luppa[5]



Professor Jürgen Popp[1,2,3]

Meet the authors – with numbers linked to affiliations:

1. Leibniz Institute of Photonic Technology (Leibniz IPHT)
2. Friedrich Schiller University Jena, Institute of Physical Chemistry and Abbe Centre of Photonics
3. InfectoGnostics Science Campus
4. Jena University Hospital (UKJ)
5. Klinikum rechts der Isar der TU München, Institute for Clinical Chemistry and Pathobiochemistry

EUROPEAN HOSPITAL

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

www.healthcare-in-europe.com

Editor-in-Chief: Brenda Marsh
Art Director: Olaf Skrober
Editorial team:
Wolfgang Behrends, Sonja Buske
Senior Writer: John Brosky
Executive Director: Daniela Zimmermann
Founded by Heinz-Jürgen Witzke
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Correspondents
Austria: Michael Kraßnitzer, Christian Pruszinsky **China:** Nat Whitney
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Germany: Anja Behringer, Annette Bus, Walter Depner, Cornelia Wels-Maug, Holger Zorn
Great Britain: Brenda Marsh, Mark Nicholls.
Malta: Moira Mizzi
Spain: Melisande Rouger, Eduardo de la Sota
The Netherlands: Madeleine van de Wouw
USA: Cynthia E. Keen, i.t. Communications, Lisa Chamoff

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Representatives

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

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

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

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

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

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

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

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

Despite its power, validation remains challenging

Relating AI to biomarkers

Using artificial intelligence (AI) to push development of imaging biomarkers shows great promise to improve disease understanding. This alliance could be a game changer in healthcare but, to advance research, clinical validation and variability of results must be factored in, a prominent Spanish radiologist advises.

Report: Mélisande Rouger

In clinical practice efforts are already ongoing to apply AI to obtain new imaging data and improve the stepwise development of radiomics and validation of biomarkers, Professor Luis Martí-Bonmatí, Head of Medical Imaging at La Fe Polytechnics & University Hospital in Valencia, told delegates at the ESR AI Premium event last April in Barcelona. 'There's a mass of imaging data obtained daily and waiting to be deciphered and analysed to understand what's happening in every patient across the huge diversity in people, diseases and disorders,' he pointed out.

Using genomics, proteomics and metabolomics, scientists can already unveil biological processes in an individual patient. Computational medical imaging enables evaluation of tissue properties and behaviours from medical images, to accurately describe things relevant to a patient at a specific time. Using computerised modelling, mainly thorough deep learning techniques, high-dimensional data can be extracted and mined to build descriptive and predictive diagnostic tools. Highly performing computational techniques, such as Convolutional Neural Networks (CNN), help to provide new information on tissue expression diversity from 'real world' imaging studies, making a noticeable contribution to advancing healthcare.

'If we can implement computer-based processes designed to analyse medical images to depict and classify those tissue changes, with their value and distribution, we might have a nice tool in our hands to improve personalised medicine using medical images,' Martí-Bonmatí said.

Not every radiologist is familiar with biomarkers, yet they could transform radiology clinical routine and deeply impact on healthcare. Biomarkers are similar measures to those obtained from blood samples; they may indicate biological processes, pathological changes or pharmaceutical responses. When biomarkers are imaged, subrogated features and parameters can be obtained that will give quantitative information on regional distribution of these changes whenever necessary. In other words, tissue changes can be depicted over time and located, meaning they are resolved in both space and time. As images do not harm the organs and lesions, researchers can evaluate heterogeneous distribution of whatever they want to look at, whenever they want to look at it.

Biomarkers can be used to diagnose phenotyping, so to detect or confirm the presence of a disease, or to identify different diseases sub-types and even different habitats within a single lesion. They also can be used to assess why a tumour is responding to treatment, whilst other identical tumours are not, and to measure susceptibility to potentially develop a disease.

When linked to treatment effect, biomarkers can have predictive value not only on therapy effectiveness, but also safety, by looking at the extent of toxicity, a well-known adverse effect. 'Ideally, we could also have biomarkers on prognosis and help determine likelihood of disease recurrence or progression, or patient survival, by taking a look at the lesions and organs where the abnormalities are present right at the beginning of treatment decision to predict which therapy will work best,' he suggested.

In daily practice, huge amounts of images are generated from different modalities and sequences, using a broad diversity of information channels for acquisition. Image preparation, including registration, analysis, resizing, intensity normalisation and tissue segmentation, are the next step. 'We need to virtually 'take out' the organ or tumour we want to evaluate, to check what happens in that tissue as automatically as possible. Once we obtain this volume of interest,' he said, 'we can move to picture feature attributes, which is mainly radiomics, and go into morphology or semantics, spatial distribution of signal intensity, and histogram distribution, with all the different texture features that can be obtained across organs and tissues.'

Dynamic model parameters can also be used in the region or volume of interest, by calculating values that might describe what is happening in a given lesion through histograms, distribution statistics or spatial distribution of feature metrics.

A huge amount of data has been generated at this stage, so efforts must focus on reducing data, and then applying statistics or multivariate analysis or classifiers like clustering signatures. 'We might be lucky and link whatever we have here with the diagnosis, predictive or prognostic endpoints that are our interests,' Martí-Bonmatí said: 'And then we will have biomarkers.'

Obtaining biomarkers is not an easy task and external validation in the clinical setting is key. 'The relevance of those imaging findings and their correlation with the clinical endpoints and the impact on healthcare pathways must be shown,' he pointed out. For example, in texture analysis of liver metastasis, some parameters might enable classification of lesions into those that will respond and those that won't, right from the onset of treatment. 'That's quite good for us.'

But the big challenge remains future variability – unavoidable because image acquisition parameters still differ from one examination to another. 'If we slightly change repetition time, echo time, flip angle, slice thickness on an MR sequence, the obtained parameters will change. Processing techniques, methods, filters, quantification levels and image depth will also change the radiomic features,' he said. 'So, small changes in so many variables will change the results.'

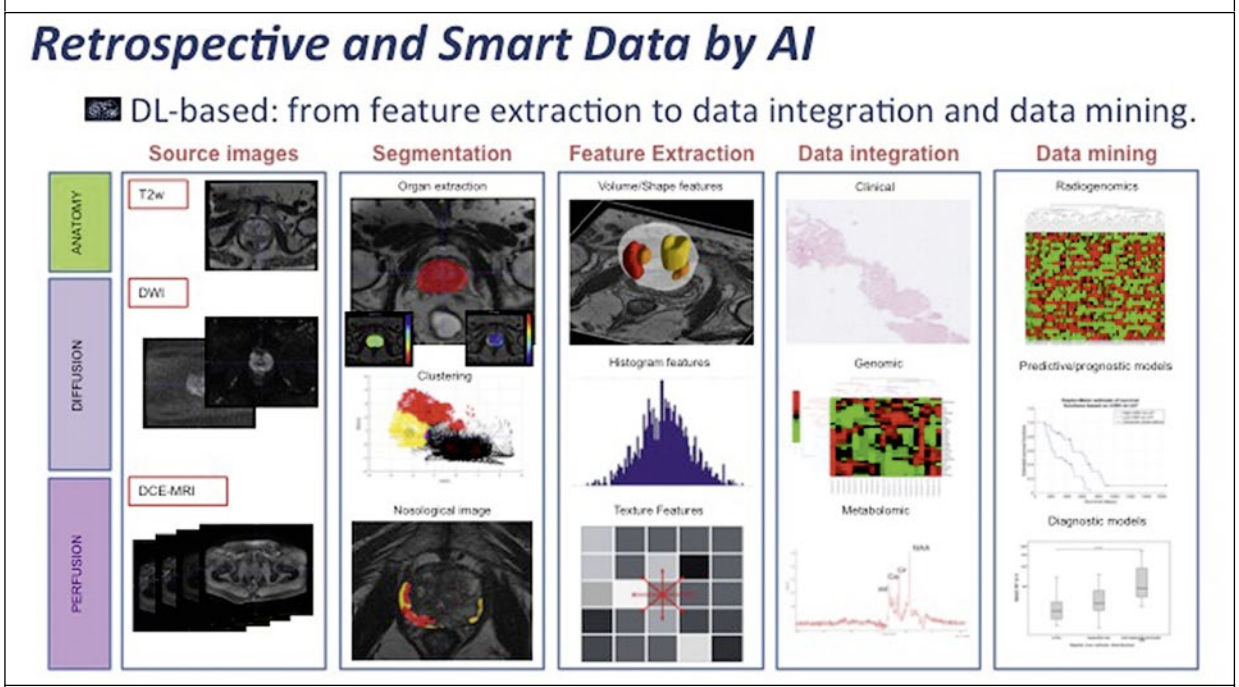
Signal dynamic parameters in MR techniques, such as intravoxel incoherent motion on diffusion-weighted sequences, may offer additional parameters that can be linked to aggressiveness of prostate cancer, for instance. But, the variability with this approach needs consideration – number, distribution and magnitude of the b-values, signal strength, amount of noise and lesion type will all impact on the calculated parameters.

Using voxel-enhanced dynamics, again in prostate cancer, the cellularity metrics obtained from the intravoxel incoherent motion, and the permeability Ktrans obtained through a pharmaco-kinetic model after contrast administration, may change widely in a clustered way. 'If we perform a multivariate, multiparameter map, we can visualise those areas with high cellularity and high vascular permeability, which are the most aggressive ones. Unfortunately, the variability using these multivariate techniques together increases exponentially,' he explained.

Therefore, researchers should ask themselves a number of questions: do they have the right and precise answers by using texture analysis or feature properties or parameters from signal dynamics? Will this process prove useful in clinical practice? Why are the best answers to the right questions still wrong?

'Wrong means that we have a huge amount of variability in what we are doing. So, we have to look for the uncertainty of our truth. And we have to recognise that for anything we measure from images to be representative of a physical reality, we must have a clear relationship with the reality we are measuring. Imaging signal comes from voxels, and voxels have a huge amount of complex inner structures, all with different properties and components, obtained with different protocols, techniques, and machines. So it's close to impossible to have a standardised image processing or image acquisition or parameters. Once we recognise this,' he concluded, 'we can work on ways to improve our work.'

Luis Martí-Bonmatí MD PhD serves as Head of the Clinical Area of Medical Imaging at La Fe Polytechnics & University Hospital, Valencia, Spain, and a member of the Spanish National Royal Academy of Medicine. He is also the founder of QUIBIM S.L. and serves as its Director of Scientific Advisory Board.



Parasites & company – what can the radiologist see?

When pathogens travel with us

Sunburn and happy memories are not the only things we can bring home from a holiday. Sometimes parasites, fungi, viruses or bacteria from distant countries accompany our return, later to become noticeable in unpleasant ways, often to pose a real health threat. At the German Radiology Congress in Leipzig, Dr André Lollert and colleagues ventured into the world of tropical and travel medicine. The senior paediatric radiology consultant at the University Medical Centre of the Johannes Gutenberg University, in Mainz, provided an overview on which of these 'stowaways' can also enter German hospitals – and how radiology deals with them.

Report: Wolfgang Behrends

In his Leipzig presentation, Dr André Lollert spoke about worms (helminths), such as Echinococcus and Schistosoma; fungi of the genus Histoplasma, and about viral and bacterial infections. These pathogens mostly enter the body by ingestion (less frequently via skin injuries) and cause a wide range of diseases. 'It's mainly increasing tourism, but also migration that bring into our hospitals diseases whose origins lie in very different parts of the world. Therefore, the probability of being confronted with these exotic diseases in clinical routine is rising.' Whilst native parasites such as fox or dog tapeworms are relatively common, the occurrence of melioidosis, a dangerous bacterial infection which is mainly found in Southeast Asia, is also on the increase.

If patients come to hospital after being abroad, these cases often can be quite harmless – the classic being travellers' diarrhoea. 'However, depending on the country the patient visited, a more exotic, differential diagnosis must be considered.' For people whose immune defence is impaired by age or illness these pathogens can be life threatening. 'Worms, in particular, move through the body once they have entered it, so different organs can be affected,' Lollert explained.

An image alone is not enough

For the radiologist, the pathogens frequently remain invisible – only the traces they leave in the body can be seen. 'Each parasite has a preferred part of the body where they settle. Whilst Echinococci often spread in the liver, histoplasmosis or melioidosis usually affect the lungs.'

Since the diseases may manifest in a very typical way, the interaction between radiology and patient anamnesis is vital, says Lollert: 'Imaging alone does not deliver

Continued on page 14

Dr André Lollert is a senior consultant in paediatric radiology as well as radiation safety officer at the University Medical Centre of the Johannes Gutenberg University in Mainz. Whilst his research focus is on paediatric radiology he also specialises in the diagnosis of metabolic and infectious diseases.
In 2017, Lollert was awarded the Publication Prize of the Society of Paediatric Radiology for his cancer research work in the field of quantitative imaging procedures.

A revolution akin to industrialisation

Today and future radiomics

Radiomics is one of the most exciting topics in radiology. It involves data and artificial intelligence (AI) but very few people know or understand the details. In her lecture 'How does Radiomics work?', presented at the German Radiology Congress in Leipzig, Professor Ulrike Attenberger, Vice Chair and Medical Director from the Institute of Clinical Radiology and Nuclear Medicine in Manheim University Medical Centre, Germany, outlined how radiomics will advance radiology but also the obstacles faced along the way.

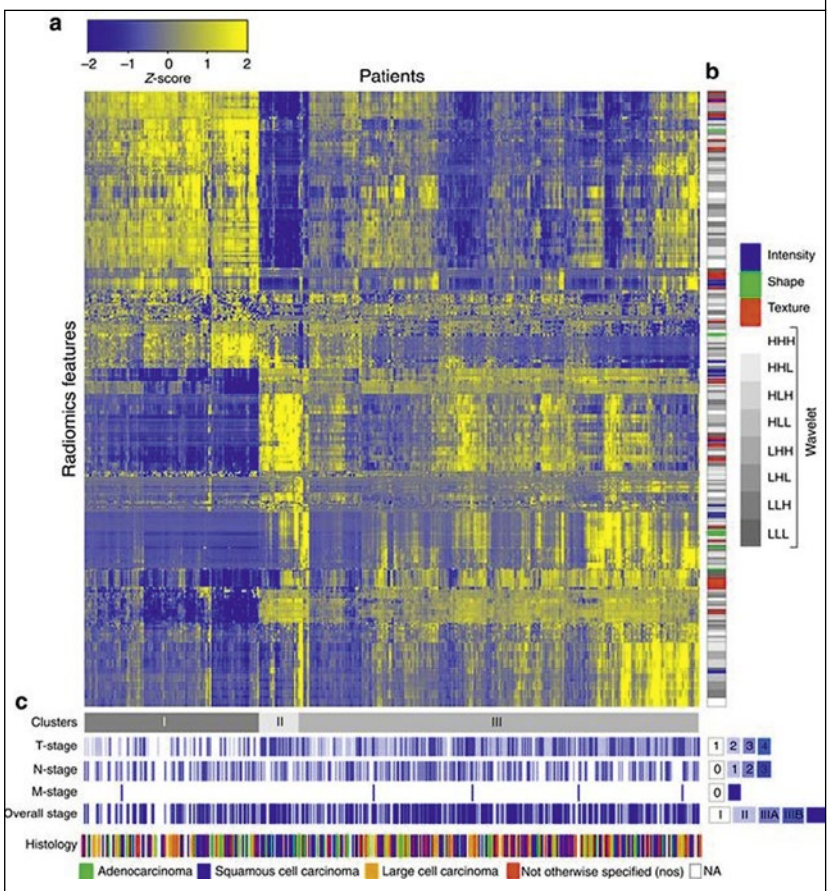
Report: Daniela Zimmermann

Images become numbers – The central idea behind radiomics is the extraction of standardised, quantitative, multidimensional information from CT or MRI image data sets using artificial intelligence procedures.

Obtaining standardised, quantitative information from images is currently a key issue. 'The evaluation of radiological images still depends on the individual experience of the radiologist.' In the case of liver lesions, for instance, criteria that are not particularly tangible, such as the uptake behaviour of a contrast agent, are being used. Laboratory values, on the other hand, can be quantified as numbers, and thresholds clearly distinguish between normal and pathological values. 'In radiology, we only really have this to a very small extent,' Attenberger points out.

This is where Radiomics comes in. With the help of AI procedures, quantitative information is extracted from image features which can then be integrated and evaluated with clinical, molecular and genetic data. 'It is hoped that this will allow a more precise prediction of clinical endpoints than is currently possible with individual analysis of image features.' The ability to quantify image features in a standardised way is a basic prerequisite of personalised medicine. This is needed to develop image-based biomarkers.

This happens with Radiomics Workflow: 'Medical image features are extracted, analysed and modelled to predict treatment-relevant targets – such as progression – and survival rates, or the response of a tumour to certain types of therapy.' Researchers have discovered the potential of this technology not only for oncology but also for analysis in cardiac imaging. Radiomics applications already improve the differentiation between calcified and non-calcified plaques and enable better identification of patients with acute myocarditis.



Radiomics heat map:
(a) Unsupervised clustering of lung cancer patients (Lung1 set, n=422) on the y axis and radiomic feature expression (n=440) on the x axis, revealed clusters of patients with similar radiomic expression patterns. (b) Clinical patient parameters for showing significant association of the radiomic expression patterns with primary tumour stage (T-stage; $P<1 \times 10^{-20}$, χ^2 test), overall stage ($P=3.4 \times 10^{-3}$, χ^2 test) and histology ($P=0.019$, χ^2 test). (c) Correspondence of radiomic feature groups with the clustered expression patterns.
Source: Hugo J. W. L. Aerts, Emmanuel Rios Velazquez, Ralph T. H. Leijenaar, Chintan Parmar, Patrick Grossmann et al.: Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach; Nature Communications (https://www.nature.com/articles/ncomms5006); © 2014, Springer Nature

Attenberger is convinced that, for Radiomics to exhaust its full potential, new skills must be taught during specialist medical training – such as dealing with statistics and software programming: 'In the future, radiological training will have to include a lot more Maths and computing, as well as close cooperation with disciplines like medical computation, bioinformatics etc.'

From diagnostician to machine trainer

To a certain extent, radiomics is the further development of computer assisted diagnosis (CAD), the radiologist adds: 'It's a very structured procedure; instead of visual classification on the basis of a lesion, a firm analysis algorithm, which begins with the segmentation of a region of interest (ROI), is used. Special algorithms then extract characteristics from this, such as texture and shape analysis, or histogram distribution. This can be used independent of the imaging modality.'

The importance of Radiomics

'This is a revolution comparable to the industrialisation in the 18th and 19th centuries,' Attenberger says. 'We need to completely rethink and change our diagnostic routines.' The image itself is no longer at the centre, but the training of a machine, or an algorithm respectively, which extracts information from image features that is not apparent to the human eye.

The computer can create heat maps and correlate the information generated from the image with clinical data such as outcome, disease progress or genetic data and laboratory values. 'This is a very complex, multistage process where statistical procedures play an important part. Although it may seem paradoxical, many features become reduced during this process, but this is necessary to avoid overfitting, i.e. over-adaptation due to accounting for too many variables, sometimes barely relevant to the issue. The results of this "training" are then validated using new sets of data.'

The Holy Grail and the black box

Consequently, at the end of this calculation there are figures that describe how precise the trained model is, to deliver conclusions as to how aggressive a tumour is, for instance, or how well it will respond to a certain treatment. The latter is not easy to determine, the expert explains: 'This is still a bit of a Holy Grail. Initially, we have to model how the tumour is likely to change during treatment. The details of quantifiable changes before and after therapy must then be correlated with other variables, such as genetic or clinical data. We can then, in theory, derive a predictive model which can potentially deliver predictions on effectiveness.'

However, as yet this approach is nowhere near ready for clinical application. First, unified standards must be determined that can be used to edit new data. 'We've actually seen some progress here, not least due to projects such as the Image Biomarker Standardisation Initiative (IBSI) or the Radiomics Quality Score Initiative from Professor Lambin in Maastricht.'

AI could be another way to balance the heterogeneity of the protocols, which is currently making a universal use of analysis procedures impossible. Before any approaches to this become established one of the most prominent demands from experts is to reveal the source codes of the algorithms in large databases, so that the procedures can be made repeatable.

Professor Ulrike Attenberger is Vice Chair and Medical Director at the Institute of Clinical Radiology and Nuclear Medicine at the Manheim University Medical Centre. After gaining her medical degree in Munich 2006, her doctorate followed on the 'Importance of MRI in the diagnosis of pulmonary hypertonia'. Her research focus is now on MRI, for example its use in tumour diagnosis, and the evaluation of therapy response. The professor received a Fellow Award from the RSNA for her work on the optimisation of dose reduction for contrast-enhanced MR angiographies. She also received the Walter-Friedrich Prize from the DRG (German Society of Radiology) for her habilitation thesis on the implementation and evaluation of new acquisition and processing procedures to expand MRI applications in routine clinical diagnostics.

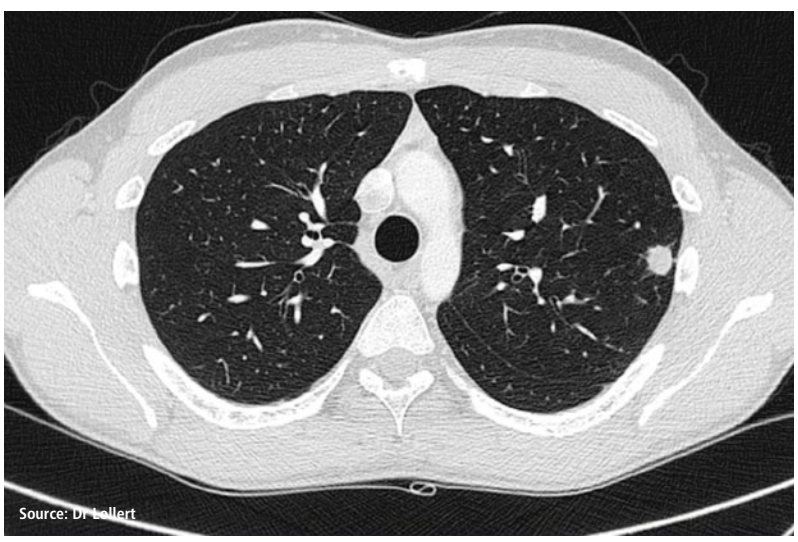
When pathogens travel with us

Continued from page 13

a reliable diagnosis. The region a patient visited provides important clues as to which pathogens could be the cause.' If necessary, pathology or microbiology can provide confirmation via biopsy.

Talking to the patient, as well as taking the patient's symptoms into account, can also indicate which imaging procedures should be used. 'If an Echinococcosis with neurological symptoms is suspected, the procedure of choice would be an MRI scan of the brain. In the abdominal region, the typical liver cysts that develop after a parasitic infestation can be visualised with ultrasound. The imaging modalities are as diverse as the possible pathogens.'

Radiological findings also affect treatment. Whilst some pathogens can be surgically removed, in other cases patients are treated with antibiotics or antihelminthics. Imaging procedures can also be used to monitor the effectiveness of this treatment.



This CT image shows lungs damaged by histoplasma fungi. The radiologists has to read into these traces to identify the parasite.

Climate change drives vectors north

Along with travel, other factors also spread exotic diseases, Lollert added. 'Global climate change makes it possible for certain types of mosquito to move further north. These insects often transmit diseases that have, until recently, hardly been found in Europe.' As yet, there have not been any significant clusters of these vector-borne diseases in Germany; but, he said, the transmission vectors could become more relevant in the future.

Multiscale integrative cross-disciplinary imaging

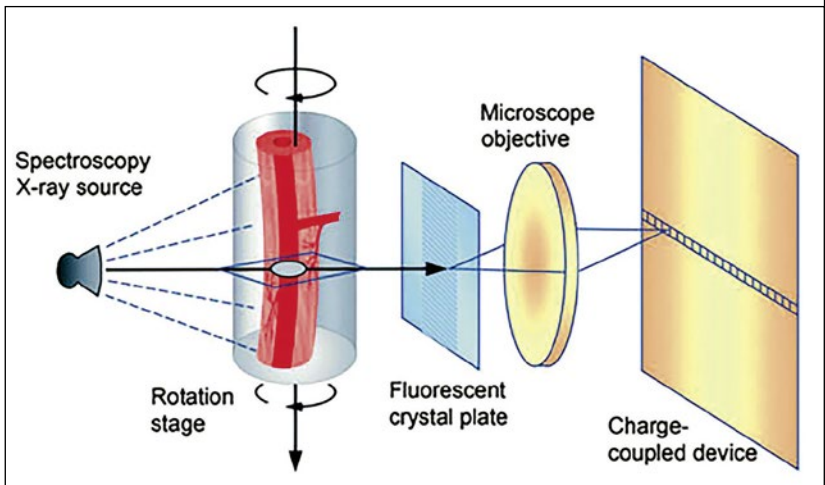
Modernising diagnostic medicine

By Willi L Wagner and Hans-Ulrich Kauczor, from the Translational Lung Research Centre (TLRC), University of Heidelberg, Heidelberg, Germany

Pathologic-radiologic correlation is already utilised in various settings as a tool to assess the interpretive performance of imaging studies and identify radiologic features corresponding to histologic findings. However, correlative assessment is currently limited mainly to the fields of research and quality assurance, and is generally not a routine element of the radiologist or pathologist workflow.

Under the current paradigm of diagnostic medicine, pathologists and radiologists operate as members of distinct disciplines. Diagnostic radiology localises and characterises pathological conditions and informs about clinical-stage and potential comorbidity determinations. Pathology denominates specific lesions histologically while providing insights into immuno-characterisation and molecular features. Hereby, the diagnostic dyad has a spectrum of multiparameter techniques at its command that allow for a scale-spanning assessment from the entire organism over whole body cavities and single organs, or lesions to their forming tissues and molecular signatures of single cells.

In the context of rapidly emerging technical advances in both fields, and the trend to offer ever more specific parameters, the current practice of reviewing separate pathology and radiology reports in the limited setting of the hospital's tumour boards may not be sufficient, because the responsibility to correlate and integrate the diagnostic data all too often falls on the treating clinician.



Schematic diagram of the microcomputed tomography device (micro CT). CCD = Charge-coupled device.
Source: Gössl M, Bentley M, D, Lerman L, O: Review – 3D Micro CT Imaging of Renal Micro-Structural Changes. Nephron Clin Pract 2006;103:c66-c70. doi: 10.1159/000090611; © S. Karger AG

Pathologic-radiologic discordance can result

Because both disciplines' data are essential to making correct diagnoses and facilitate appropriate decision-making to funnel the best patient management possible, an isolation of pathology and radiology workflows, can be detrimental to the quality of patient care. Independent reporting of findings and a lack of communication can result in pathologic-radiologic discordance with the clinician left with the task of reconciling the diagnostic conflict. A direct linkage between pathology and radiology workflows and an integration of diagnostic data may prevent bifurcations in interpretation and reporting.

The benefits of an integrated multidisciplinary approach have recently found expression in the latest clinical practice guideline on the diagnosis of idiopathic pulmonary fibrosis (IPF) by the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society, and the Latin American Thoracic Society.

Diagnosing IPF is often highly challenging

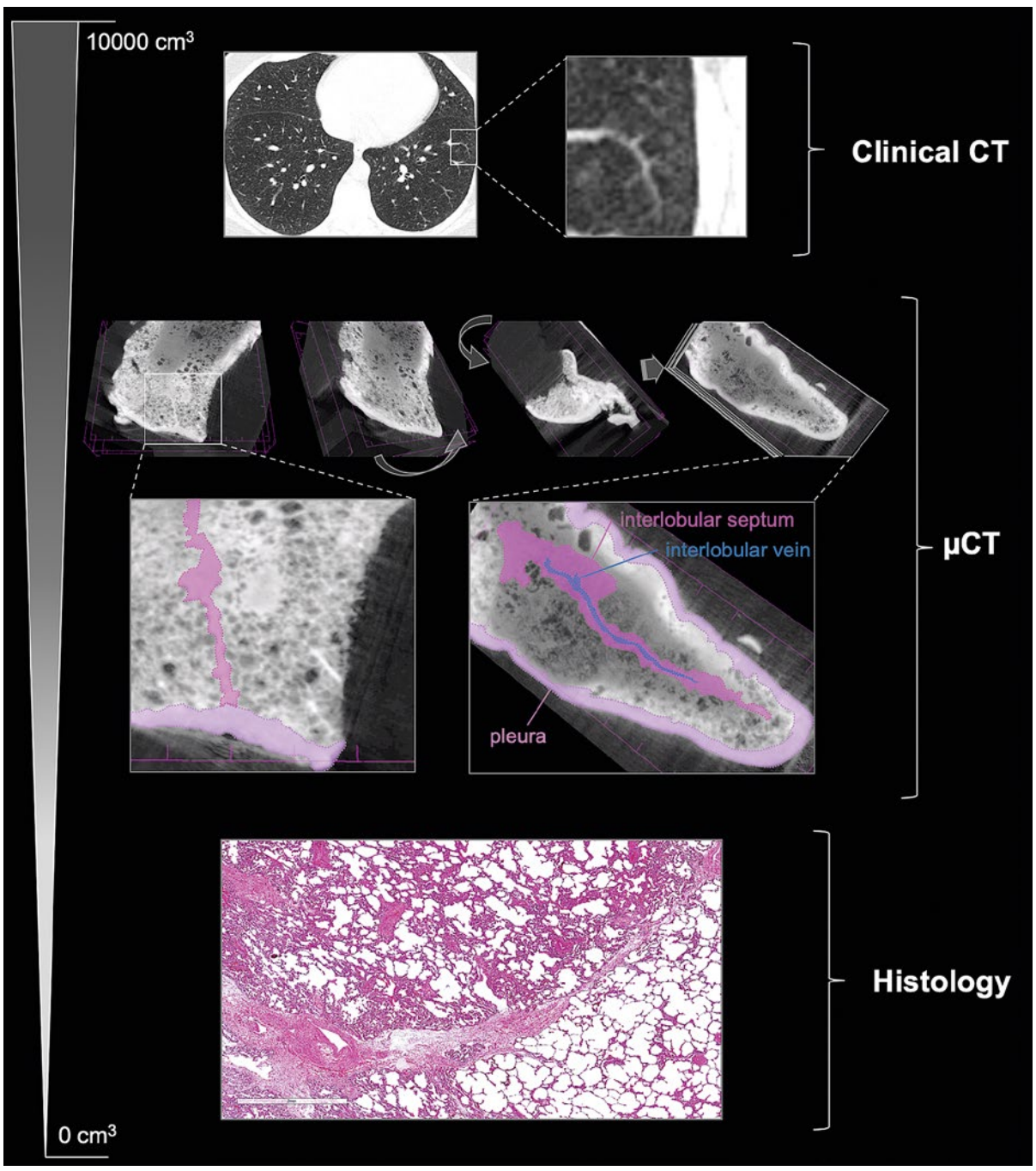
IPF is a specific form of chronic, progressive, fibrosing interstitial lung disease (ILD) of unknown cause and particularly poor prognosis. The committee places ILD experts in a 'multidisciplinary discussion' in the centre of the algorithm for the often highly challenging diagnosis of IPF: 'IPF is diagnosed if the appropriate combination of HRCT patterns and histopathological patterns are present. (If no potential cause for ILD is identified)'. In this setting both pathology and radiology can overturn one another in the diagnosis of IPF. Only a dynamic, integrated interaction between pathologist, radiologist and clinician can specify the biological behaviour and prognosis of complex conditions such as interstitial lung disease.

A convergence of workflows between pathology and radiology may be driven by the need for detailed three-dimensional information on the composition and architecture of surgical specimen and biopsies. Microcomputed tomography (µCT) is a high-resolution X-ray based imaging modality commonly used in industry and material science and is emerging as a powerful tool in preclinical and translational biomedical research.

Operating at the interface of the organ and tissue scale µCT imaging can provide a global map of the excised specimen in a non-destructive manner. Whether used on a fresh, fixed or paraffin embedded specimen, µCT can add useful topographical data that can be mapped back to the radiological in situ imaging studies and serve as a coordinating system for planning the histological work up. Such imaging studies will have to be evaluated both by members of the pathology and radiology department. Such profound diagnostic teamwork on a daily basis would benefit the development of integrated diagnostics.

The increasing digitisation of pathology workflow, from analogue slide microscopy to whole-slide imaging scanners and pathology picture archiving and communication systems, paves the way for integrated cross-disciplinary information technologies. Comput- ational advances based on quantitative digital image analysis, e.g. artificial intelligence and deep learning algorithms, will further break down disciplinary borders.

As medicine becomes increasingly specialised, there is a need to integrate complex multiparametric diagnostic information into coherent representations to establish a diagnosis, determine prognosis, drive patient management and yield efficient medical decision making. Rapid technological advances occurring in both fields offer an opportunity to develop a scale spanning, integrated, diagnostic system that facilitates the synthesis of data produced by both specialties and therefore, improves the overall quality of patient care.



Scale-spanning integrated assessment of pulmonary veno-occlusive disease (PVOD). Clinical CT shows smoothly thickened interlobular septa and geographic and nodular ground-glass opacities while offering an assessment on the whole-organ scale at a spatial resolution of 500µm. µCT can fill a missing gap in terms of high-resolution three-dimensional non-destructive imaging, here depicting a thickening of the visceral pleura and marked irregular thickening of an interlobular septum with a pulmonary vein at its core at a spatial resolution of 9µm (isometric voxel size). Note the possibility of virtual slicing and free reorientation of the volume dataset in space. Histology confirms fibrotic thickening of the interlobular septum and fibrotic narrowing of the peripheral pulmonary vein.[1]

Prof. Dr. Hans-Ulrich Kauczor studied medicine in Bonn and Heidelberg in the late 1980s and then worked as a research assistant at the Department of Radiology at the German Cancer Research Center (DKFZ), returning there later in his career as head of this department from 2003-2007. He completed his doctorate at the University of Cologne and his habilitation at the University of Mainz. He has been Professor for Diagnostic Radiology at Heidelberg University since 2003, becoming Medical Director of the Radiology Department in 2008.

Willi L Wagner is a resident, research associate and assistant lecturer at the clinic for diagnostic and interventional radiology of the University Hospital Heidelberg. His research focuses on the detection and therapy of pulmonary diseases. International activities include medical electives and research stays in the USA and Australia. He has been awarded, among others, the "Rising Stars" scholarship of the European Society of Radiology and the teaching award of the Johannes Gutenberg University Heidelberg.

1 Lavinia Neubert et al., "Comprehensive Three Dimensional Morphology of Neoangiogenesis in Pulmonary Veno Occlusive Disease and Pulmonary Capillary Hemangiomatosis," The Journal of Pathology: Clinical Research 5, no. 2 (March 25, 2019): 108–14, doi:10.1002/cjp2.125.

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