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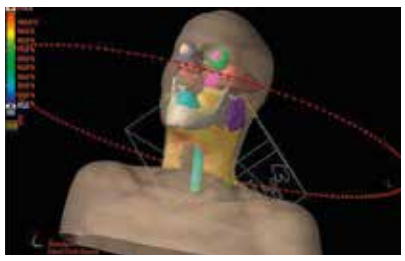

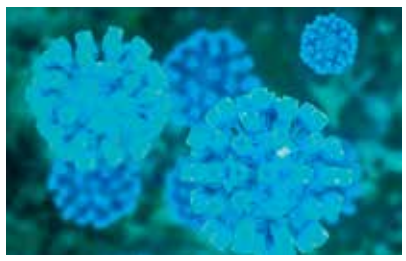

Ebola: Reports of panic among medics

Experts confirm the disease can be contained by stopping the chain of infection

Report: Michael Krassnitzer

By definition, an emerging infectious disease is one that has newly appeared in a population or has been known for some time but is rapidly increasing in incidence or spreading to new geographic areas.

At the International Meeting on Emerging Diseases and Surveillance (IMED 2014), in Vienna, this year's focus was on one particular emerging infectious disease: Ebola. According to the World Health Organisation (WHO) in the recent outbreak 5,400 people have died of this dangerous disease and, as of 20 November 2014, more than 15,000 cases were reported in eight countries.

'This most serious Ebola outbreak ever was caused by social, geographic and political factors in the regions affected,' says Belgian physician Hilde De Clerck MD, who works for the aid organisation Médecins sans frontières in the crisis regions. All severely affected countries are poor, have underdeveloped health systems, were involved in wars or armed conflicts in the past few years, and the people tend to mistrust government agencies and the countries mistrust each other.

De Clerck: 'The epidemic started off slowly and spread quickly, affecting people from all walks of life. Lack of awareness about the disease, insufficient protection measures and the high degree of mobility of the people between three of the countries concerned – be it for business or family purposes – contributed to Ebola being able to spread.' There is, however, good news: Oyewale Tomori DVM, PhD, President of the Nigerian Academy of Science, describes how Ebola was contained in his country. On 20 July 2014 a person from Liberia with acute Ebola symptoms arrived at Lagos International Airport. The preliminary diagnosis – Ebola – was confirmed by a private hospital. This index case had had contact with 72 people at the airport and in the hospital, who potentially were exposed to the virus.

Source: MSF; Julien Rey

Médecins Sans Frontières medics: a vital aid organisation in crisis zones

The Ministry of Health and the Nigeria Centre for Disease Control (NCDC) declared an Ebola emergency. On 23 July the Ministry of Health, the regional government of Lagos and international partners set up an Ebola crisis intervention centre.

The index case died on 25 July 20. Subsequent Ebola infections were reported in Nigeria. All of them could be traced back to the index case. Close to 900 identified contact persons were monitored; eight patients died. On 20 October 2014, WHO officially declared Nigeria Ebola-free.

'It is to a large extent due to the quickly established crisis intervention centre that we were able to successfully fight the disease,' said Tomori. 'We not only suffer from a real epidemic in West Africa, we are also suffering from an epidemic of fear that's spreading all over the globe,' said Dr Pamela Rendi-Wagner, Director of the Department of Public Health Services and Medical Affairs at the Austrian Federal Ministry of Health and adds, 'Despite concerted efforts by all public health authorities it is difficult to counter the rising public panic'. In Austria it was reported that several health professionals quit their jobs because they feared having to care for Ebola patients. 'It is our main task to listen to these fear-driven concerns and to inform and communicate widely, openly, early and in a transparent fashion in order to create trust,' the health official emphasised.

Experts agree on one issue: they consider screening of in-coming travellers at international airports for Ebola to be useless, inter alia because usually people with an acute Ebola infection cannot travel. During the severe acute respiratory syndrome (SARS) pandemic, in 2002/2003, 45 million travellers were screened at airports – with only a single SARS case being identified.

It is much more important, according to the experts, to use the money for aid programmes right in the affected regions. 'It is crucial to provide help where the epidemic broke out, that is in Western Africa,' underlines Jack Woodall MA PhD, an epidemiologist from Brazil and vice-editor of ProMED-mail, the web-based Programme for Monitoring Emerging Diseases of the International Society for Infectious Diseases (ISID). He is confident: 'We can stop the disease from spreading if we manage to break the chain of infection.'

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Seeking best practice

Lisa Chamoff reports on a US lab that rapidly formed anti-ebola skills

On 29 July, Dr James Ritchie was attending the American Association of Clinical Chemistry's annual conference in Chicago when he received the call that a physician and missionary worker, who had been in West Africa, were headed to Atlanta's Emory University Hospital.

Nearly four months later, Ritchie, an associate director of the core and toxicology laboratories at the hospital, shared some of the lessons he and his staff learned in eventually treating four ebola patients. During a webinar hosted in November by the American Association of Clinical Chemistry (AACC), he explained: 'Laboratory testing … was what really made the difference between the treatment they would received in the U.S. compared to the treatment they would have received in West Africa, where they were stationed.'

Emory University certainly had a leg up in handling the virus. The facility's Serious Communicable Disease unit was established in 2003, after the facility was approached by the U.S. Centers for Disease Control, also based in Atlanta, about providing a place where workers could come if they contracted a virus in the field, or had an accident at one of their laboratories.

Lab staff was comprised of four different medical technologists, all point-of-care (POC) coordinators who trained every six months. Ritchie said they used a completely isolated facility instead of the main lab for testing, out of an 'abundance of caution', and because it was available, though he notes that a dedicated lab is not required when working with ebola.

Protective clothing and an observer's surveillance

Of course, caution was also taken when interacting with the patients. Lab workers, as well as nurses and doctors, would first go into a clean anteroom, put on paper scrubs and plastic shoes in a locker room and then don protective gear before going into the patient's room. There was always a safety person, who was nearly suited up, looking on in case there was an accident. After leaving, the visitor would remove their gloves, wash their hands and doff their PPE in a special 'hot area,' before going into the locker room to shower. Even with so much already in place, the facility needed to be flexible. In the lab, with doctors requesting more and more tests, they had to expand from one particular chemistry rotor to a whole family of chemistry rotors. Something Emory lab workers also found useful was a fully automated PCR instrument from BioFire Diagnostics, which was used a lot to monitor respiratory, GI and blood culture infections to rule out other diseases the patient may have had.

Communication was the key in coordinating testing, Ritchie said. At Emory, the lab technicians started out taking verbal orders from the physicians, but after a lot of miscommunication, with things getting done that weren't ordered and vice versa, they switched to a paper requisition that the nurse or doctor filled out. There was a team meeting every morning to review plans and protocol and there were many open forums and town hall meetings.

'It's very important that every member of the team knows what's expected of them and what's going to be happening during the day,' Ritchie pointed out. Staff in the area also had their temperature taken twice daily and had to answer questions about symptoms, which continued for 21 days after their last shift in the unit via the web. As the first community hospital in the United States to admit an ebola patient, staff at Texas Health Presbyterian Hospital, Dallas, also found that communication was important in handling the virus. Beverly Dixon, medical director in the hospital's department of pathology and laboratory medicine, offered a list: 'Communication to the nurses to control times of testing and draws and allowable testing; communication to the doctors who would like to order everything in the EMR lab catalogue, which can't really be done and turns out it isn't necessary anyway; communication to staff in a manner that allows you to post lab menus so that they could know exactly what can be done.'

When the patient first came to the hospital, she said, they didn't know he had ebola and the facility handled the specimens in the standard way, with 'no negative outcomes.'

More stringent decontamination of instruments

The second time, to rule out other illnesses, they ran the specimens using standard universal precautions, but with more stringent decontamination of instruments. There were two workers furloughed for 21 days, who were found to not have used standard precautions properly. Ultimately, 38 people were monitored.

The facility did switch from standard universal precautions to using much more stringent PPE, which made staff feel much safer in handling the specimens, she said. Dixon advises labs to perform a risk assessment to figure out appropriate protocol and equipment for that facility. She recommends a template for public health risk assessment for the ebola virus that is available on the Association of Public Health Laboratories website.

Dixon also recommended taking a mock specimen and running through the handling process. 'During that observation, you'll see things you would never have thought of while you were sitting there at a desk versus walking through the actual procedure on an instrument with a mock specimen.'

Dr James Ritchie, associate director of the core and toxicology laboratories at Atlanta's Emory University Hospital

Handling waste and shipping specimens

Something Emory wasn't prepared for was the amount of medical waste the patients generated. Ritchie said two patients generated a total of 350 bags, or about 3,000 pounds, of medical waste.

Shipping specimens is also a big issue. While Emory University Hospital was lucky enough to have the CDC down the street, laboratories do need to plan a shipping strategy. Peter Iwen of the University of Nebraska Medical Center, noted that the facility found it challenging to arrange shipment of ebola samples with a courier, and ultimately ended up spending $1,900 per sample. 'This was not an easy thing to do,' he explained.

Samples are required to be shipped as Category A infectious substances, which meant the person packaging the sample and the courier had to be certified. Once you have an ebola positive patient, the CDC will provide guidance, but the shipping issue will likely be a challenge. 'You need to have this relationship with your public health laboratory,' Iwen said. 'You need to work out details of how you're going to get samples from a patient that might be in your emergency department, who you are trying to screen or rule out ebola virus infection.'

EU: Mo

Jane McDougall reports on preliminary findings from the EU funded initiative striving for greater equality in healthcare systems across Europe.

The European Commission has an ambition to create more equitable, cost-effective and available healthcare throughout its member states. Dr François Meyer, International Advisor to the French Haut Autorité de Santé (HAS) presented results from one EU initiative, collaboration between HTA agencies (EUnetHTA), set up to help achieve these aims at a recent meeting organised by MAPI, a service provider to the global healthcare industry.

Health technology assessment is a multi-disciplinary field of policy analysis that studies the medical, social, ethical and economic implications of development, diffusion and use of health technology. It bridges the gap between the world of research and the world of decision-making.

In terms of Europe today, healthcare systems are financed and organised at the national level with inter-

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re equality in healthcare

Dr François Meyer, International Adviser to the French Haut Autorité de Santé (HAS)

ventions evaluated by national HTA bodies using criteria, procedures and rules that are defined at that national level. This means that across member states there are differences in HTAs' processes; the only common obligations being to take decisions based on objective and verifiable criteria and the respect of timeframes e.g. 90 or 180 days for a new drug. This means that, in Europe, there are country specific differences in access to health technologies complicating cross-border healthcare.

In fact, two major models are used in Europe. One, used in countries such as France, is based on determination of added clinical benefit, which then leads to price negotiation and a final decision. In other countries, such as the UK, a health economics analysis using the price proposed by a company is instigated and then the decision is based on the calculation of the estimated cost/QALY and this is then compared to the threshold acceptable for the country's policy makers.

The licensing of drugs is already carried out at a pan-European level by the EMA, so why not go further and have a centralised approach to HTA? The EUnetHTA Joint Action 2 Grant Agreement has been in place since 1 October 2012 and is scheduled to run for three years.

Thirty-seven partners in 26 EU Member States are involved in the project, which focuses on strengthening the practical application of tools and approaches to cross-border HTA collaboration to establish a sustainable structure for HTA work in the EU.

To convert this into reality and ensure that all European citizens have best possible healthcare now and in the future, with resources allocated according to need rather than economic climate, two types of collaborative action have been attempted. As Dr Meyer explained during his presentation, the first is to cooperate on HTA production. Its aims are to avoid duplication of work (e.g. between 2005 and 2008, seven HTA reports on drug eluting stents were produced) and increase consistency and transparency.

To achieve these, joint assessment reports of core HTA information have been created, as have templates for companies to submit data and methodological guidelines for HTA bodies to follow. A concrete example of this collaboration is the methodological guidelines put in place for the assessment of the relative effectiveness of a new drug. In this case nine guidelines have been put in place to be followed by HTA bodies when assessing a drug. They cover the choice of end points, comparators and comparisons and levels of evidence.

The second type of collaboration is a project to improve the quality of data produced in primary research. The objectives of this initiative are to improve the development plans of new technologies and the additional data collection (to reduce uncertainty after initial assessment). The tools put in place to help obtain these are 'early dialogues', disease specific guidelines and a definition of common core protocols for the collection of additional data.

An on-going example is the development of disease specific guidelines for osteoarthritis; the draft document will be available for public consultation later this year (Q4).

Early dialogues are an initiative whereby the company presents its development plan and ask questions to HTA bodies to check whether the choices made are appropriate (e.g. the choice of comparator, endpoint, population and so forth).

The completely confidential meetings are funded under the umbrella of EUnetHTA and another European initiative, SEED (Shaping European Early Dialogues) which is coordinated by the HAS, France. These meetings are attended by between to five to 12 different HTA agencies with the EMA invited as observer. To date, 14 different projects for new drugs have undergone early dialogue with great success in improved efficiency and six more projects are about to enter the process.

Despite the apparent advances from this EU sponsored model many questions remain unanswered. How will the European cooperation on HTA be financed in the long term? Will there be a fee for service for some activities? How will HTA bodies work together in the future? Which HTA bodies will participate? What will be the priorities of the permanent HTA network? How will national HTA bodies used the joint work for the production of their national HTA reports?This October, these vital questions were addressed and debated at the HTA 2.0 Europe conference in Rome.

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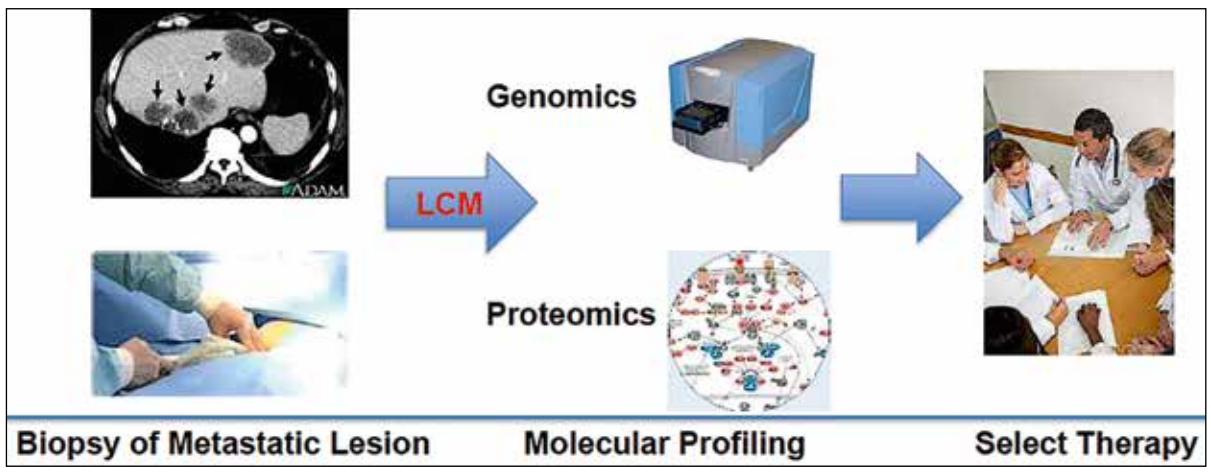


Molecular genetics and proteomics

Women with metastatic breast cancer know they have a slim chance of long-term survival. The question is whether personalised therapy could extend their lives, asks Cynthia E Keen

The combination of molecular profiling and proteomics to create individualised breast cancer treatment is continuing to show promise, with the results of the second Side Out clinical trial published online 11 September 2014 in Breast Cancer Research and Treatment.

Proteomics is the use of molecular biology, biochemistry, and genetics to analyse the structure, functions and interactions of proteins produced by the genes of a particular cell or tissue. Proteomic tests provide information that genetic analysis cannot. Genetic analysis can identify all the proteins that a tumour is capable of making. Proteomics measure the activity levels within the signalling pathways of individual tumours – pathways that drive the growth, activity and reproduction of cancer cells, and thus identify the proteins that are responsible for tumour growth.

The two pioneering Side-Out clinical trials conducted between 2010 and 2012 created individual therapies for women with advanced breast cancer metastases who had already received multiple treatments. Their objective was to determine if individualised treatment could produce better outcomes than their most recent treatment – and they did.

'Genomic sequencing and proteomic pathway mapping of metastatic lesions have recently shown that the molecular factors driving the growth or drug resistance of metastatic colonies may be quite different from the primary tumour from which they are derived. What this has meant is that conventional treatments may not be very effective, as evidenced by the fact that metastatic breast cancer patients tend to undergo a series of different consecutive treatments, each with diminishing effectiveness,' said Professor Lance A Liotta MD PhD, co-director of the Centre for Applied Proteomics and Molecular Medicine at George Mason University in Fairfax, Virginia, USA.

Dr Liotta discussed the Side Out trials, of which he is a co-investigator, with European Hospital. These were sponsored by the Side-Out Foundation, a U.S. organisation of volleyball players and coaches dedicated to making significant and identifiable differences in the lives of breast cancer patients. He has spent much of his career investigating the process of tumour invasion and metastasis at the molecular level.

'These trials are exciting because this is the first time that treatment for metastatic breast cancer has been individualised. Participants' metastatic lesions were biopsied and profiled. A multidisciplinary treatment selection committee then reviewed the patient's data, and recommended therapeutic options based on the molecular findings. The most effective drug or drugs identified were either donated by pharmaceutical companies or paid for by the foundation,' he said.

Lance Liotta co-directs the Centre for Applied Proteomics and Molecular Medicine at George Mason University, VA.Fairfax, VA

'Our primary objective was to determine if the individualised therapy would produce 30% longer time to progression as compared to the patient's most recent prior treatment. A secondary objective was to determine the percentage of time that the patient's oncologist would have selected a different treatment than that selected by the investigators.'

21 patients participated in Side-Out I, six of whom had partial responses and 12 had stable disease. The disease control rate was 72%. Forty percent experienced 30% or longer time with a progression-free response. Side-Out II treated 25 patients, who had had undergone anywhere from three to 12 prior treatments. Five had partial response and eight had stable disease. An addition 4% – or 44% of the total experienced 30% or longer time with a progression free response. Significantly, none of the physicians of any of the patients had selected the treatment that was actually administered.

'This type of individualised therapy shows huge promise,' Liotta confirmed. The Side Out Trials target Future research that stems from the Side Out Trials may greatly benefit metastatic breast cancer patients by identifying and delivering the most likely effective treatment as soon as metastasis is identified. At a minimum, this could eliminate treatments that won't be effective because of the molecular differences of the metastatic lesion compared to the primary one.

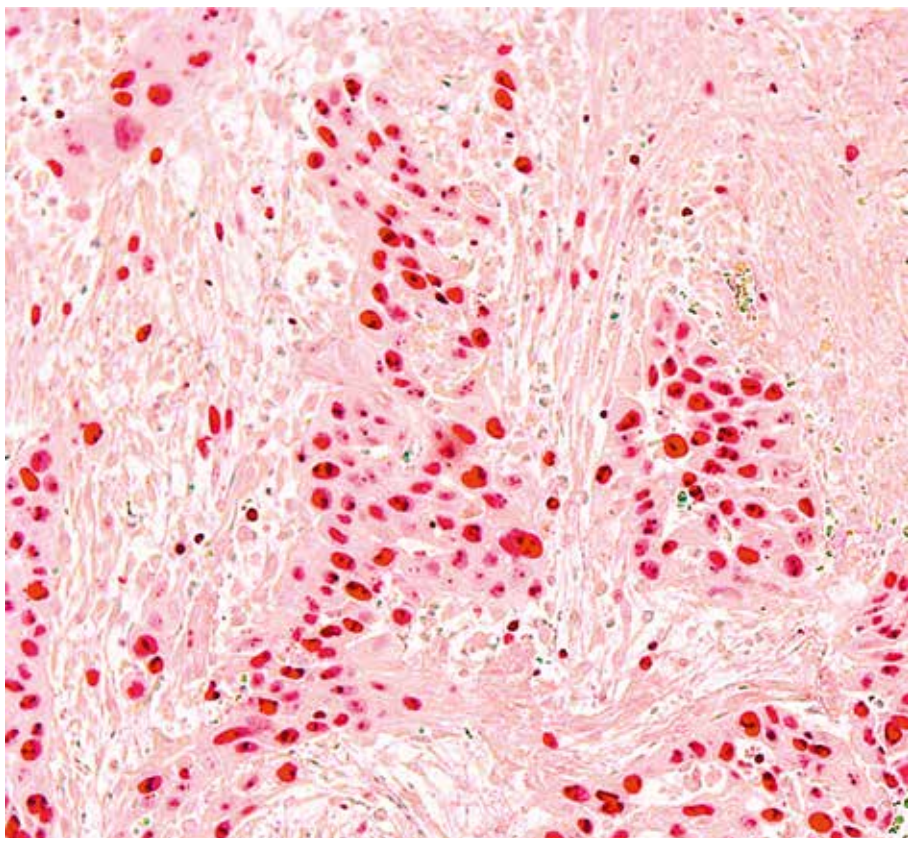
On the other end of the time course of cancer, Dr Liotta and his colleagues are currently conducting a breast cancer trial aimed at stopping breast cancer before it starts. The PINC trial (Preventing Invasive Carcinoma with Chloroquine) is a neo-adjuvant trial accepting all patients diagnosed with ductal carcinoma in situ (DCIS). Women with a biopsy diagnosis of DCIS receive a one-month oral dose of an anti-autophagy inhibitor before surgical therapy of their DCIS lesion.

The advantage of the DCIS trial design is that the DCIS lesion size and proliferation index can be compared before and after therapy in the same patient, so the therapeutic outcome is known immediately.

The team hopes that cancer treatment centres in Europe will consider enrolling. The future goal is to develop a short-term oral therapy that kills breast cancer precursor lesions to prevent breast cancer.

Outwitting cancermecha

Immunotherapy using synthetic long peptides,



The human immune system is usually very efficient in protecting the body against diseases by eliminating pathogens as well as infected, damaged or otherwise suspicious cells. However, it often fails because tumours have developed efficient strategies that hamper the system's ability to detect and destroy the cancer cells.

For example, certain structures on the surface of immune cells, such as T cells, act as regulators of the immune system, so that T cells can be prevented from attacking healthy tissue. Cancer cells often produce enzymes and ligands able to manipulate these regulators. In this way they can de-activate T cells that are directed against characteristic structures on the surface of cancer cells. The T cells lose their ability to bind to the tumours cells, and thus no action against the tumour is initiated.

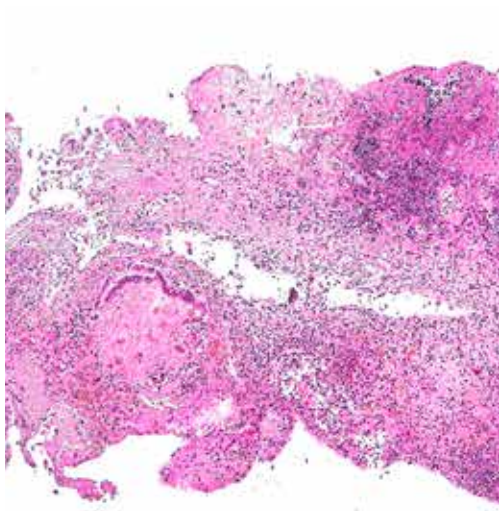
Most recently, new drugs have been approved that can remove the brakes that tumours apply to the immune system. Antibodies blocking the negative regulators of the immune system, the so-called 'checkpoint inhibitors', are tremendously successful because they restore the body's spontaneous anti-tumour immune response. One example is Yervoy ipilimumab, a monoclonal antibody targeting CTLA-4, a protein receptor that down-regulates the immune system. These drugs lead to response rates of up to nearly 50% in various cancers.

Even though these figures are impressive, not all treated patients have their spontaneous anti-tumour immunity restored. Additionally, because the drug leads to a general activation of the immune system, some patients experience autoimmune side effects.

Fortunately, however, new strategies to overcome those limitations are in development. One approach aims to address and change the tumour's immune environment. 'We are delivering modulating signalling molecules to the micro-environment of tumours and infected cells,' explains Dr Frank Schnieders, CEO of Provecs Medical GmbH in Germany. 'Once present in sufficient concentration, they restore the vulnerability of diseased cells and activate the body's own defence mechanisms locally and systemically.'

A local, transient expression of these factors for a few days, is sufficient to mount a lasting, systemic immune response against the diseased cells, resulting in the elimination of tumour cells, or of cells harbouring the pathogens, Schnieders adds. A first product, IM01, is in late preclinical development to treat bladder cancer and already licensed to an undisclosed pharmaceuticals partner.

At the end of November, researchers from Dutch firm ISA Pharmaceuticals introduced a different approach in Nature: With a team from the Washington University St. Louis they analysed the T cells unblocked by the checkpoint inhibitor drugs and the structures the T cells were directed against. This led to the discovery of two interesting new antigens on the surface of tumour cells.



Tissue section of a human bladder tumour. Islands of dividing tumour cell (stained red) surrounded by normal bladder wall cells indicate a severe cancer stage

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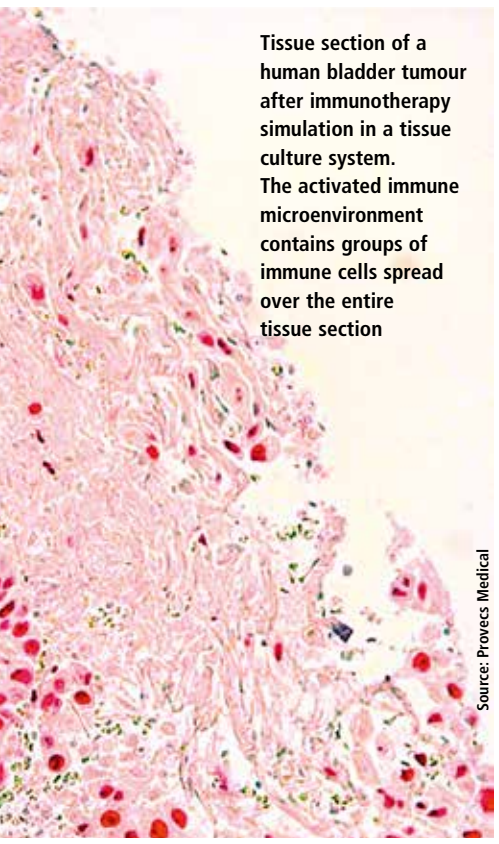
Ludger Weß reports



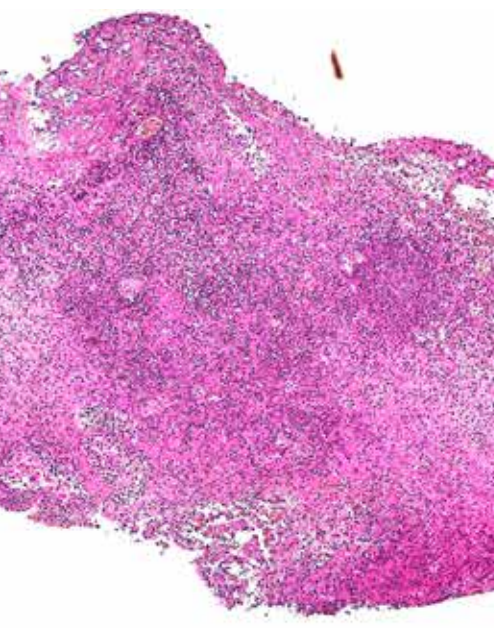
Source: Provecs Medical

Tissue section of a human bladder tumour after immunotherapy simulation in a tissue culture system. The activated immune microenvironment contains groups of immune cells spread over the entire tissue section

In a second step, the scientists demonstrated that a mixture of two synthetic long peptides (SLPs), each incorporating one of the mutant amino acid sequence and an adjuvant, were able to eradicate the tumour as effectively as checkpoint immunotherapy.

'These findings offer important mechanistic insights into the mode of action of checkpoint immune regulators, and point the way towards personalised approaches based on the SLP immunotherapy concept,' said Professor Cornelis Melief, Chief Scientific Officer of ISA and a co-author of the paper. 'Checkpoint blocking is capable of activating existing inert T cells against mutant antigens. Now we know that an adjuvanted SLP-based immunotherapy, with similar anti-tumour effects to checkpoint immunotherapy, can be created.'

The preliminary successes of cancer immunotherapy clearly demonstrate the potential of this approach. Most likely, a combination of various strategies will in the future lead to even higher response rates and less side effects in treating cancer.



Tackling mobile tumours

Precision radiotherapy with 4-D imaging

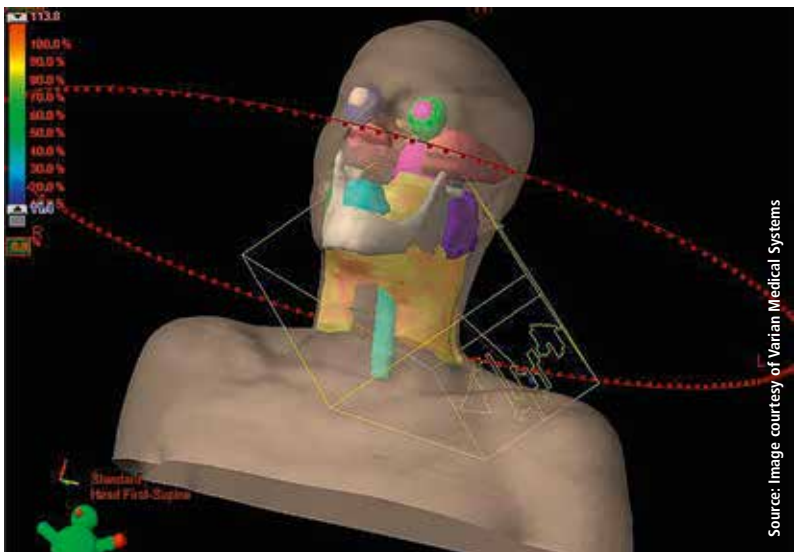
Report: Chrissanthi Nikolakudi

Radiotherapy always encounters particular challenges when a tumour is 'mobile'. This is when radiotherapy must be carried out over several weeks. Within that period the tumour position, shape and expansion typically will keep changing. Thus radiotherapy needs continuous adaptation to maintain continuously precise radiation.

The treatment of lung cancer and of tumours located in the upper abdomen is at particular risk of missing the tumour and therefore endangering treatment success, because these tumours change position by several centimetres due to a patient's natural breathing. Up to the 1990s there was no method to account for this movement in radiation calculations, so the patient had to be given expanded radiation.

Classic radiation therapy based on 3-D spatial resolution only captures the tumour's position, shape and expansion and then targets it. Speaking at the 20th Annual Congress of the German Society for Radiation Oncology (DEGRO), Professor Matthias Guckenberger, specialist for Precision Radiotherapy and Director of the Clinic for Radiation Oncology at the University Hospital Zurich, explained: 'If the 4th dimension, i.e. time, comes into play because of tumour movement then conventional treatment is no longer sufficient and we need 4-D radiotherapy.'

4-D radiotherapy is also known as Stereotactic Body Radiotherapy or Stereotactic Ablative Therapy. This non-invasive procedure depends on imaging procedures such as CT, MRI and PET/CT to locate the tumour precisely. 4-D CT then facilitates individual and precise measurements of the tumour movement for each patient.



Source: Image courtesy of Varian Medical Systems

Treatment plan for a 4-D radiation therapy

Based on the extent of the movement of tumours in the upper abdomen, for instance, a strategy to compensate for the movement is then selected. 'If the tumour moves by more than 5-10mm, 4-D radiotherapy is needed,' Guckenberger said. The physician then has a number of procedures and technologies available to target the highly mobile tumours precisely. 'One of these,' he explained, 'is to use gating, that is, to stop radiation whenever the tumour moves from its focal point. Once it moves back into its original position radiation is then resumed.

'In the case of tracking, the radiation moves dynamically and in synchronisation with the tumour, i.e. it always pursues it,' he added. 'There are different procedures that are all equally as good. The important thing is to decide on one procedure and then to implement it consistently, with experience and quality assurance.'

In practice, the treatment team, of doctors, physicists and radiographers, carries out this treatment in three steps. First, the extent of tumour movement is calculated during the radiotherapy-planning meeting. Next, the radiation is adapted to this movement. Finally, radiotherapy, adapted to the patient's breathing, commences.

4-D radiotherapy fights tumours affected by respiration movement with high doses. 'This is a big advantage of the procedure: the treatment is intensive, but short, Guckenberger pointed out. 'The procedure has a lower risk of side effects and can be carried out on an out-patient basis.'

Matthias Guckenberger MD, is director of the Clinic for Radiation Oncology at the University Hospital Zurich, Switzerland. Following his habilitation on 'Image Guided Precision Radiotherapy', in 2012 he gained the professorship for Radiotherapy at the Medical Faculty of the Julian Maximilian University of Würzburg, Germany.
The professor also manages the Working Group for Stereotactic Body Radiotherapy for the German Society for Radiation Oncology (DEGRO).

Results from stereotactic body radiotherapy performed at 13 German and Austrian treatment centres are also consistently excellent. Small lung cancers can be treated so effectively with the aid of 4-D radiotherapy that the clinical results are comparable with those achieved through surgery.

This also enables successful treatment of patients who cannot undergo surgery due to concomitant diseases.

Stereotactic body radiotherapy is now increasingly also used to treat liver and kidney cancers as well as spinal metastases – with very promising results.

Deepening knowledge of the cancer genome

The term 'cancer' describes more than 200 different diseases and every single one needs to be clearly understood and requires, ideally, individual treatment. To do this we need to deepen our understanding the cancer genome. 'In the ageing population the 'cancer' diagnosis increases but, thanks to modern medicine, mortality decreases,' declared Professor Christof von Kalle, Speaker of the Board of the National Centre for Tumour Diseases (NCT) at the German Cancer Research Centre (DKFZ) in the Helmholtz Society during the European Cancer Research Congress in Munich. Anja Behringer reports.

Dr von Kalle, who heads the NCT Translational Oncology Department, is particularly pleased with the excellent technological facilities that will advance interdisciplinary personalised cancer medicine above all in genomics, proteomics, imaging, radiotherapy, immunology and prevention. Today patients' tumour cell genes can be analysed to design a custom-made therapy.

Beyond primary tumour cells, metastases have become a major object of interest in cancer research. For decades scientists have assumed that the protein coding is the most important – if not the only – function of the genome, with the genes providing the necessary 'coding plan'. Surprisingly, however, only about two percent of the genome is indeed protein-coding sequences while 98% do not carry any coding information at all. Nevertheless, 70-90% of the genome is translated into the language of the messenger: ribonucleic acid (RNA). These non-coding RNA molecules, copies of the genome without protein codes, are important products of the genome.

Members of the Helmholtz junior researcher group 'Molecular RNA Biology & Cancer' at Heidelberg University Hospital focus on this 'young' class of molecules. The scientists assume that they play an important role in cancer development and therefore might be important biomarkers or target structures for therapies.

Dr Sven Diederichs, Head of the junior researchers group, reports that they could link one of these non-coding RNA molecules to lung cancer progression. The RNA is associated with the development of metastases – the cause of death in the majority of patients who suffer lung cancer, responsible for more deaths worldwide than any other type of cancer.

The German Cancer Research Centre DKFZ in Heidelberg

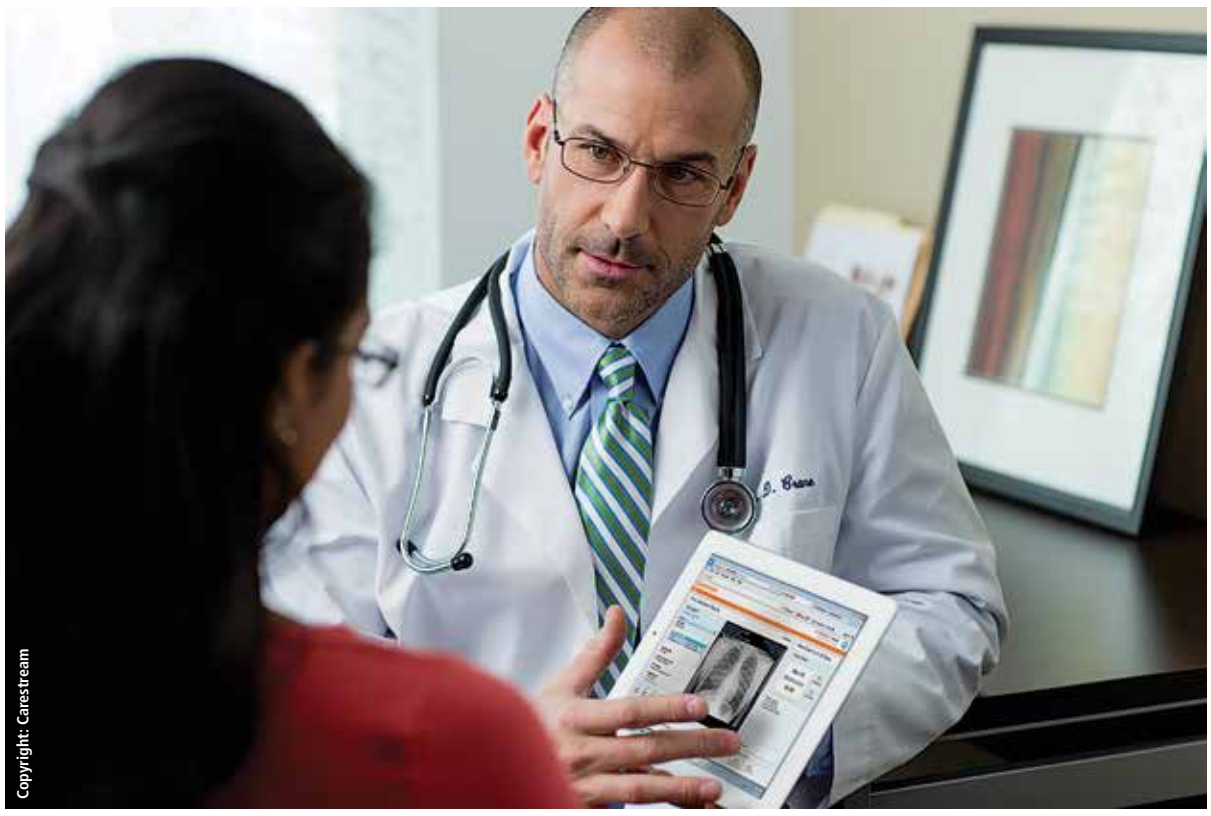
The Clinical Collaboration Platform

Opening archives for wider access during planning or consultancy

'Customers tell us vendor neutral archiving is a great way to store their images, but they ask what good it is unless they can then access those images where and when they want for planning clinical pathways, or in consultancy,' explained Christine Kao, Marketing Manager for Global Healthcare IT at Carestream.

During RSNA 2014, Carestream showed it could push vendor neutral archiving (VNA) beyond data warehousing by launching its Clinical Collaboration Platform, reported to be better at gathering, managing and sharing clinical data. 'It starts by giving a broader capability to embrace data that is often scattered across a healthcare enterprise, some of it perhaps sitting in a cloud, sometimes just sitting in a camera in a clinic. There are videos from surgery, slides from pathology, digitised ECGs and photos taken by a dermatologist. All of this needs to be captured,' Kao explained.

The Clinical Collaboration Platform employs Carestream's intelligent Vue Archive to archive and exchange clinical content in DICOM, but also goes beyond the traditional capabilities offered by a VNA in accepting non-DICOM formats. Files are managed in their native format without conversion. 'We don't care where a file came from, and the platform can accept any file,' said Kao. 'Once it is captured and tagged with meta-data, it can then be share with multiple collaborators through a web-based tool that can be loaded onto any web-enabled device.'


Copyright: Carestream

After capturing and archiving patient data, the Clinical Collaboration Platform offers two further modules for enterprises to manage and distribute the data.

Again without reinventing an organisation's practices, Carestream can embed the zero-footprint Carestream's Vue Motion media viewer into an existing electronic medical record (EMR) to maximise the ability for physicians to collaborate.

The Clinical Collaboration Platform is also workflow neutral, Kao said. 'A doctor continues to see patients as always; he takes photos as he always has and with the same equipment. What Carestream brings is a way to help manage that data while seamlessly integrating with an existing IT ecosystem and clinical workflow.'

Cooperative collecting of patient data helps break down walls between ancillary departments, sites and networks to provide physicians with a single view of critical patient records.

Embedding Carestream's Vue Motion zero-footprint viewer into an organisation's EMR can maximise the ability for physicians to collaborate. Physicians can conveniently access 3-D/MPR images, interactive reports and video streaming from their mobile devices or workstations.

In terms of healthcare departments maintaining their autonomy while sharing a common workflow, Carestream demonstrated its 'data ingestion workflow' via mobile devices as part of a work-in-progress linked to this platform. The company also demonstrated added native reporting capabilities to capture clinical notes as a part of this approach.

'Equipping clinicians and patients with a new generation of clinical content capture and review workflow tools delivers a more holistic view of the patient's condition and can lead to better treatment decisions,' Ludovic d'Aprea, General Manager for Global Healthcare Information Solutions at Carestream, pointed out

Fast Forward to digital radiography

Breaking down the last barriers against conversion from analogue or hybrid digitised CR to DR

Report: John Brosky

Agfa HealthCare is accelerating the shift to digital X-ray by enabling any radiology clinic to convert at its own speed and within its own budget with innovative and market-leading solutions.

'There is no hurdle anymore for any customer to move from analogue X-ray to digital radiography,' said Jan Leeuws the Business Unit Manager for Digital Radiography (DR) at Agfa HealthCare. Under an umbrella programme called 'Fast Forward', Agfa HealthCare is bundling a portfolio of products to be presented at RSNA 2014 that enables radiology departments to affordably advance on a customised path that leads to the overwhelming benefits of DR for higher quality images at a significantly lower dose.


Image: Agfa Healthcare

Agfas's DX-D 40 digital detector with Automatic Exposure Detection (AED) offers a fast and easy way for radiography facilities to benefit from high-quality digital imaging using any X-ray equipment

'The move to DR brings as many benefits to the healthcare provider as it does to patients by eliminating the dark room with all its chemistry and improving workflow,' said Leeuws. 'There is still a lot of ground to cover,' he said, adding that, despite the now clear advantages of DR, there remain a substantial number of X-ray exposures being made with direct analogue or hybrid digitised computed radiography (CR) technologies. As a result, the achievements in reducing dose in radiography are still at a very early stage.

With a worldwide installed base of close to 50,000 digital radiography systems, Agfa HealthCare is removing the last barriers against conversion to DR through the Fast Forward programme so that all healthcare facilities, regardless of size or budget, can flexibly and cost-effectively upgrade film and CR operations. 'It's a combination of highly sensitive detector panels with industry-leading processing power that allows us to reduce dose up to 60 percent over conventional plates,' Leeuws explained.

The standout in the portfolio is the newest introduction from Agfa HealthCare, the DX-D 40 auto-trigger detector that was introduced at RSNA. 'We call it instant DR,' said Leeuws, 'because installation is quick, easy and non-invasive.'

'It took us less than a half hour to set up demonstrations at different customer sites in Italy, France, Spain, the United Kingdom or the United States and, when we we're set to leave, invariably the radiologists would ask us to stay. They didn't want us taking away the demonstration panel,' he said.

The demonstration also quickly convinced users of the many advantages of the digital format. Beyond improved image quality and lower dose, these include reduced examination time, immediate verification of patient positioning, or improved accuracy of patient identification.

The DX-D 40 allows a radiology group to continue using their existing equipment. An automatic exposure detection (AED) sensor on the patient table activates the detector within a fraction of a millisecond for a true digital image acquisition.

Requiring no cable connections, installation of the DX-D 40 means the detector integrates seamlessly with virtually any X-ray system. The detector sends the acquired image either to a dedicated laptop computer or a MUSICA image acquisition workstation.

Connecting to Agfa HealthCare's next generation Multi-Scale Image Contrast Amplification (MUSICA) image processing, allows radiology centres to instantly reap the benefits of the digital format. The MUSICA combination with the DX-D 40 provides 'no-excuses' image quality with greatly increased detail, providing more diagnostic information from low dose images with a balanced presentation for visualisation of subtle features.

The next generation MUSICA, presented by Agfa HealthCare at RSNA 2013, is exam- and body part-independent, thereby providing a consistently very high diagnostic quality image. 'Installing improved technological capabilities is just one element of progress for a radiology group,' said Leeuws. 'It's not realistic to simply present staff with dose-lowering capabilities and expect them to immediately adopt a lower-dose approach. A core part of achieving dose reduction lies in the education and re-training of staff.'


Jan Leews, Business Unit Manager for Digital Radiography (DR) at Agfa HealthCare

'With DR the staff sees that every image they take is perfect, certainly better than ever before, but there is a risk of patient dose creeping up,' he said. 'Here, education is needed to show that, with these DR panels, they have such a wide dynamic range that actually allows them to further lower dose from previous exposure levels. Then to show them that, on top of this, they can apply Agfa HealthCare's image processing to bring out more detail from the image so that the dose can be lowered further.

'What is driving Agfa HealthCare is achieving the optimum balance between the lowest possible dose delivered to patients while achieving the highest level of diagnostic information required clinically to treat that patient,' he said.

Improved MRI access for cardioverter defibrillator implant patients

MorphMatch technology allows 3T scanning


Images: Biotronik

Cardiovascular technology specialist Biotronik has launched a new series of single and dual chamber implantable cardioverter defibrillators (ICDs) and cardiac resynchronisation therapy defibrillators (CRT-Ds). 'The Iperia/Itrevia/Inventra series gained CE approval in July 2014 and marked its first implantations worldwide in mid-July,' the multinational biomedical technology firm reports. 'With its ProMRI technology, Biotronik is the first and only company to offer heart failure patients CRT-Ds and leads that can undergo MRI scans. Patients with single-chamber ICDs can take advantage of 3Tesla MRI scans with an exclusion zone. Both single and dual chamber ICD patients are eligible for 1.5T full-body scans.'

To track the MR state of implantable devices, the firm also recently launched ProMRI SystemCheck.

Dr Klaus-Jürgen Gutleben, internal medicine and cardiology physician at the Heart and Diabetes Centre in North Rhine-Westphalia, where 200-300 patients receive CRT implants annually, intends to provide patients with CRT solutions approved for MRIs. 'MRI diagnostics are very important for my younger patients, who are better off avoiding radiation from X-rays or CT scans and patients with comorbidities like brain tumours, which are best diagnosed with high-resolution images,' he explained. 'For such patients I'd recommend an implant that can undergo MRI scans, such as the Iperia CRT-D and the Sentus QP lead.'

The Sentus QP lead eases the implantation process by giving physicians better access to challenging vessels. Sentus QP represents the industry's first quadripolar left-ventricular lead to be approved for MRI use, the company reports. 'It offers stable lead positioning in the coronary sinus and various electronic repositioning options to select the optimal stimulation site.'

Dr Gutleben: 'When deciding on the right device for my heart failure patients, I want to ensure they will benefit as much as possible from cardiac resynchronisation therap. Clinical evidence demonstrates that patients have reduced mortality when they receive fewer inappropriate shocks. We also know it can greatly improve their mental well being and satisfaction with the therapy. Detection criteria and morphology analysis help to ensure my patients only receive the therapy they need.'

'The new ICDs reduce inappropriate shocks with MorphMatch morphology detection criteria and optimised anti-tachycardia pacing (ATP), making it easier to give a patient exactly the level of pacing therapy he or she might need,' Biotronik explains. 'While delivering shocks at the right time can save patients' lives, minimising shocks improves patients' quality of life.'

Wolf Ruhnke, Vice President at Biotronik, also added that the IN-TIME study demonstrated that Biotronik Home Monitoring reduced heart failure patients' mortality by over 50 percent.

Patients with ProMRI defibrillators can undergo MRI scans

Imaging 'difficult' patients

Oasis 1.2T MRI has powerfully expanded

Hitachi has double-downed its bet on the advantages of open-platform MRI by introducing a new generation of the Oasis 1.2T scanner this year at the RSNA. The jump to new processing power and the new Origin 4.0 MR Operating Software effectively enhances capabilities with a range of new applications for neuro, orthopaedic and vascular imaging, as well as enhancing routine exams for women's health and oncology, John Brosky reports.

Meanwhile, Hitachi has ramped up production facilities to meet a growing demand for the unique open-platform configuration that helps radiology groups meet the challenges posed in imaging children, the disabled, overweight patients or simply anxious patients uncomfortable with claustrophobic conventional scanners. Hitachi expects to increase the availability of the Oasis platform, specifically with a focus on European hospitals and imaging centers.

The first thing you notice about the Oasis 1.2T is the wide, open patient platform, a welcome change from the sliding tables of traditional MRI designs where the patient is pushed into a confining bore. For radiologists, putting at ease these difficult patients means reducing the risk of repeat scans, decreased scan time and a higher quality diagnostic image. 'Open Architecture is a truly valued and complementary tool for healthcare providers that have an array of scanners but see this flexibility as an essential requirement for their service offering to patients,' said Shawn Warthman, Director for MR Marketing with Hitachi America.

In America today, he said, roughly one in 10 patients arriving for a diagnostic exam are obese and often too difficult to be effectively scanned in closed bore systems. The open gantry and wide table of Oasis that can accommodate all patients independent of their body size and weight appeals to what Warthman called, 'a rather large group of customers performing routine exams from large regional medical centers to smaller community hospitals.' According to Keiichi Yusa, Vice President and Director of the MR/CT Division for Hitachi Europe, 'These patients may be challenging, but they are still patients with medical conditions that require an MRI examination. Oasis allows imaging centers to perform these exams more comfortably and effectively.'

Keiichi Yusa, Vice President & Director of the MR/CT Division, at Hitachi Europe

Shawn Warthman, Director of MR Marketing, Hitachi USA

During RSNA 2014, Hitachi presented the expanded applications available for Oasis 1.2T with the combination of the new Vertex II computer and the Origin 4.0 MR Operating Software. Enhanced computing and processing power with a state-of-the-art 64-bit host computer streamlines the entire imaging process and related workflows from patient registration through scan planning, the scanning operation itself and on to image processing and image management.

Expanded clinical capabilities include 3-D isotropic acquisitions (isoFSE), combined multi-echo gradient echo imaging, radial imaging combined with parallel acquisition, or Adage and Rapid Radar and advancements in non-contrast MRA (VASC-FSE).

According to Warthman, neurology imaging benefits greatly with increased power behind motion compensation technique Radar that is available for any sequence or coil in any plane. The upgraded Oasis 1.2T now features susceptibility weighted imaging (SWI), also called blood-sensitive imaging that plays an important role in neurological exams. Spectroscopy and perfusion are also available for full clinical investigation of neurological patients.

Hitachi has also expanded its portfolio for musculoskeletal examinations by taking full advantage of the open platform architecture to acquire an image radially. While patients may try to hold still during an exam, many will voluntarily or involuntarily move. Spine examinations supported by the flow and motion compensation technique of radial acquisition with Radar, significantly improve image quality and expedite interpretation without constraining or sedating patients.

The limited availability of the early versions of Oasis, due to production constraints, means that, for Europe, the unique platform remains a relatively new scanner, according to Hitachi's Yusa. 'The advantage is that we are bringing to European centers state-of-the-art capabilities with upgraded processing power and jumping to the latest features of the version 4 software,' he said.

The new Open Architecture Superconductive Imaging System (Oasis) 1.2T

With traditional MRI the patient is pushed, on a sliding table, into a confining bore

Oasis 1.2T MRI has an open patient platform

Images: Hitachi Medical Corporation

Medica: Wearable sensors

Despite the hype, this technology is still only at the gateway towards mainstream healthcare

Report: Cornelia Wels-Maug

Wrist-watches, wrist and arm bands, tags, finger rings, clips, smart glasses, shoes, insoles, smart patches (as thermometers), sensors woven into fabrics for T-shirts and socks and, of course, implantable devices as well as ingested pills were displayed by 23 exhibitors in the Wearable Technologies Show at Medica this year.

Among physiological, biochemical and motion sensing technologies there was even an entire laboratory solution for home monitoring, with Fraunhofer Institute of Technology demonstrating how patient tracking can be implemented. This platform, developed and tested by researchers at Fraunhofer FIT, with the Berlin-based Charité hospital, T-Systems and other international partners, uses non-invasive sensors and other technology to sample blood and determine specific markers in blood, aiming to monitor cardiac diseases among the elderly at home.

Wearable sensors to measure vital parameters can be connected to this platform, which collects the various sensors' data for internet transmission to a patient's caregiver for analysis. Should the data exceed or fall short of a particular threshold, caregivers can intervene if necessary. Using an app on his/her smartphone, the patient can read the measurements along with the clinician's instructions.

Yes, given diminishing healthcare resources, the prospect of caregiving becoming more effective due to mobile sensors looks promising; yet their use – although much hyped by the 'quantified self' movement – is far from a familiar feature in healthcare institutions. 'I'm still critical about the use of wearable sensors in healthcare, because the regular incorporation of sensor data into a clinical information system is not straightforward,' cautions Markus Stein, Head of Patient Management at Ethianum, an almost fully digital clinic in Heidelberg. 'The development of interfaces is complex and therefore expensive.

'This is further complicated because there is no data standard for vendors of mobile sensors and service providers. As a result there are only proprietary interfaces that must be tailored to each healthcare provider, leading invariably to a cost explosion,' he adds.

In addition, there is the inherent risk that a battery-powered wearable sensor runs out of energy while monitoring a patient.

Are there any real uses of wearable sensors in medical care? Stein: 'The use of digestible pills is probably an interesting case for wearable sensors; they are already used to gain insights into the gastro-intestinal tract.' Other than this, there appear to be very few current uses.

Researchers from the medical information sciences division at the University Hospitals of Geneva, Switzerland, work on wearable sensors to monitor chronically ill patients. Team member Frederic Ehrler PhD: 'Ageing and chronic diseases drive up healthcare costs. Self-monitoring might be an avenue to decrease the pressure on health professionals, but we need to merge the different sensors into an aggregated physiological sensors network to consolidate all gathered data to improve care.


Courtesy of Shimmer

Shimmer3 is a wearable wireless sensor that provides superior data quality, adding value to the data collection process

'In our project we use an Arduino platform, to which we connect ten different mobile sensors. This gives us a good starting point to identify problems associated with the integration of multiple sensors. Lots of work went into solving the technical problems and now we concentrate on developing solutions for specific diseases. For this, we involve many stakeholders in the process to respond best to users' needs.'

Antoine Widmer, University of Applied Sciences Western Switzerland, Sierre, explains how the university is working with paramedics in Fribourg to develop an app which, combined with Google Glasses, enhances pre-hospital care by speeding up diagnosis. 'Because every minute counts, we presently test Google Glasses with paramedics who can collaborate in real-time with clinicians in the hospital. Via the built-in camera the physician can see and hear what a paramedic witnesses and can give precise medical guidance – on mediation, for example. Another plus is that this solution allows physicians to remain in hospital where they are needed most, but they can help multiple paramedic crews. This saves time and resources.' Are there glitches in the system? Widmer: 'The hardware needs improvement: battery life is not yet sufficient, nor is the internet connection stability.'

Paul Doherty, Vice-President of Sales at Shimmer, stressed in his Medica presentation: 'Wearable technology will be one of the most important decision support systems in the future of healthcare.' However, before this can happen, industry standards must be defined to curb integration costs; viable business models are needed and a secure, smooth aggregation of diverse data sources needs to be in place. It will still take considerable time before wearable sensors become part of mainstream healthcare provision.

Medica success: DTR launches new lines for 2015

Medica is a key event in the calendar, provided the opportunity to meet customers, distributors and suppliers from around the world who are all in Dusseldorf at the same time.

Highlighting the intensity of the event and the potential business it can generate, this year DTR Medical took the largest team ever to Medica, even sharing a photo with National Health Service (NHS) expert commentator Roy Lilley who visited the stand during the show.

New launches at Medica

Regular visitors will have certainly noticed a difference this year. To coincide with Medica, the DTR Medical brand was given a new and fresh feel with extensive use of colour to differentiate the growing range of specialities the company supplies. At the same time an upgraded and refreshed website now includes a new and improved product search functionality featuring alongside a new company Blog section highlighting recent news and new developments that will interest customers.

New partners welcomed

The recognition of the need for single-use instruments expands around the world a little more each year. At the core of this is the recognition that single-use instruments bring many benefits including savings for health providers, public or private, of Time, Life and Cost or 'TLC'.

The identification of this is the start point for any new distributor who sees the potential for mutual growth and development with DTR Medical. The latest edition of the TLC brochure will help new users find the market in their country.

At Medica the team reported particular interest from new partners in Canada, France, South Africa and Thailand and would like to thank all the visitors who came to the stand.

www.dtrmedical.com

DTR Medical®

eMotio, the examination couch that reinvents the medical examination

The all-electric eMotio couch, the most efficient examination couch ever designed, should become the new assistant for general practitioners and specialists.

Promotal carried out the largest study ever conducted in medical furniture, with 200 doctors from six European countries.

The final product, the result of three years development, allows the doctor to fully concentrate on the diagnosis, whilst gaining time and space. The patient benefits from increased comfort and lower stress for a more balanced exchange.

To optimise a medical examination, the eMotio couch offers numerous possibilities as standard. Gain in time and comfort thanks to:

- Favourite positions with one press: two 100% configurable exam positions, return to welcome position, couch/chair positions
- Fast, easy surrounding access
- Clippable lamp and stirrups in only a few seconds, no need for clamps
- Optional gynaecology position, with possibility to raise the pelvis up to 105 cm (41.34 Inch)

http://www.promotal.com/en/

MIDMARK®

Early diagnosis and treatment for joint implant contamination

Periprosthetic infections: a new disease

Early diagnosis and effective therapy of periprosthetic joint infections (PJI) remain a challenge for many physicians due to the complexity and heterogeneity of clinical symptoms. As individual solutions are needed, opportunities to discuss and exchange ideas are welcome, as clearly shown during the satellite symposium on the diagnosis and treatment of periprosthetic knee infections held at this year's German Congress for Orthopaedics and Trauma Surgery (DKOU)

Prof. Rudolf Ascherl, Clinic for Special Surgery and Arthroplasty at the Hospital Medical Centre Stiftland Tirschenreuth

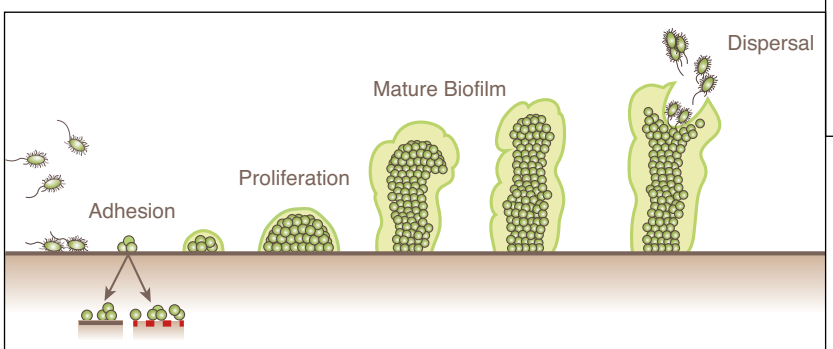
Prof. Andrej Trampuz, Section Infectious Diseases and Septic Surgery and Centre for Musculoskeletal Surgery at Berlin's Charité Medical University

Periprosthetic infections must be taken seriously – The two-year infection rate for knee replacements is currently five percent, according to arthroplasty expert Professor Rudolf Ascherl, from the Hospital Medical Centre Stiftland Tirschenreuth, joint speaker with Professor Andrej Trampuz, from Berlin's Charité Medical University.

Due to demographic developments, an increase in infection rates is anticipated; indeed the absolute number of periprosthetic knee infections is already rising. Therefore, says Ascherl, periprosthetic infections should be considered a new disease, which, to a certain extent, is unavoidable and requires specific diagnostic and therapy concepts. In addition, a stronger focus on periprosthetic infections is expedient for financial reasons since infection treatment is expensive, and the later the diagnosis is made, the higher the costs.

The 21-days rule – If an acute infection is diagnosed early, the movable parts of the prosthesis can often be preserved while late detection usually means the entire prosthesis has to be replaced. Day 21 of the infection, Trampuz explains, is the cut-off day: by now the local biofilm produced by the pathogens is too stable for the patient's immune system, or antibiotics, to be effective.

Even more importantly, individual bacteria leave the biofilm to colonise the interface of the prosthesis and the bone, thus causing a fistula or osteomyelitis around the implant. At that point, Trampuz underlines, full revision surgery becomes necessary.



The biofilm is an efficient strategy for microorganisms to survive and proliferate even in adverse circumstances. Formation and maturation: After adhesion the microorganisms proliferate on the surface – for example of an implant – and form a multi-layered 3-D structure that develops into a stable cell matrix. Due to their slow growth, bacteria in the biofilm are up to 1,000 times more resistant to antibiotics than unattached bacteria. Over time individual microorganisms leave the biofilm and transform into planktonic bacteria, which are metabolically active again and proliferate quickly.

Low-grade infection – How to deal with culture-negative infections: Diagnosing a periprosthetic infection is complicated because it can develop a multitude of symptoms. The diagnosis of a chronic or so-called low-grade infection is particularly difficult because they are often detected months, or even years, after the surgery.

Slow-growing bacteria, such as Staphylococcus epidermidis or Propionibacterium acnes, which tend to fall through the microbiology grid, frequently cause them.

Both professors recommended a joint punction with microbiological analysis of the synovial fluid and white blood cell count (concentration in periprosthetic infections >2000/ µl leukocytes or >65 % granulocytes) to confirm the infection. 'When microbiology and cytology tests are performed at the same time, the results have a sensitivity of 98 percent and a specificity of 99 percent; thus even 'low-low-low-grade' infections can be diagnosed,' Trampuz points out. However, there is one drawback: the cell count only provides diagnostically relevant information two months after the surgery.

Antibiotic therapy – Trampuz underlines that detection of the pathogen is crucial. Particularly when a low-grade infection is suspected, to be able to detect the bacterium the patient must be off antibiotics for 14 days before sampling.

As soon as the culprit has been identified a pathogen-specific antibiotic therapy can be initiated. For two-stage exchanges, both experts strongly recommended an initial local antibiotic therapy, e.g. with a revision cement loaded with antibiotics or collagen sponges, followed by systemic antibiotic therapy. 'Usually we do everything possible in terms of locally applied antibiotics, but then we go for a systemic antibiotic therapy,' Trampuz explains. In the case study he presented at the symposium, the patient with MRSA underwent temporary arthrodesis using revision cement loaded with gentamicin and vancomycin. Following the prosthesis replacement, 14 days later, and a resistance test, she received levofloxacin and rifampicin orally.

However, without extensive debridement, neither the best local nor the best systemic antibiotic therapy will be effective. Surgeons and infectious disease specialists have to cooperate to ensure the success of any periprosthetic infection therapy.

Individualised therapy – Success shows the way ahead. 'There isn't one single therapy concept that you can apply across the board, Ascherl said when summarising the tutorial. 'Rather, you have to develop your own concept that has proven to be reliable and successful.' This is where the symposium organiser Heraeus Medical provides support. The company, together with Swiss orthopaedics (SO) and the Swiss Society for Infectious Diseases (SGInf), has published the compendium 'Infections of the musculoskeletal system'.

Additionally, the educational app for iPad 'Essentials in Diagnostics of Periprosthetic Joint Infection (PJI)' from Heraeus Medical provides practical orientation based on case studies.

* The educational app can be downloaded free of charge from the App Store.
The book 'Infections of the musculoskeletal system' can be ordered free of charge in German (2013) or English (2014) at www.heraeus-medical.com

Improving contamination management

Implant and tissue infections

Report: Ludger Weß

Prosthetic joint infections (PJI) are the most frequent complication in orthopaedic implant patients and may occur any time: weeks, months, or even years after an implantation. The disease is debilitating and can develop into a life-threatening condition if not treated properly. Treatment requires the exact diagnosis of the pathogens involved and the antibiotic resistances they harbour. Based on this information, doctors can select an antibiotic and chose from a variety of treatment procedures, usually a combination of systemic treatment, local delivery by e.g. an antibiotic-releasing bone cement, and surgical procedures. Nevertheless, the failure rate is between 10 and 20 percent. Diagnosis is difficult and can take up to 14 days. One reason is the formation of biofilms on the implant's surface. These biofilms are difficult to remove and cannot be dissolved easily. Moreover, bacteria in biofilms live in a dormant state and therefore are often not detectable with conventional microbiology culture techniques.

To improve management of these infections, German molecular diagnostics company Curetis AG has developed a highly multiplexed, PCR-based lab-in-a-cartridge to enable a fast, and automated, reliable diagnosis of pathogens plus resistance genes. The disposable Unyvero i60 cartridge is covering up to 114 analytes, including pathogens that are hard to grow in culture, such as anaerobes, and many resistance markers. It needs only a few minutes of operating time and provides results in about five hours.

'The i60 cartridge adds to our Unyvero Solution, consisting of a sample lysator, analyser, cockpit and cartridges for various indications,' explains Dr Oliver Schacht, CEO of Curetis AG. 'Our Unyvero L4 Lysator is powerful enough to process biofilms and the i60 cartridge's PCR-based technology can handle and analyse small amounts of bacteria and fungi present in the sample, regardless of whether they are dormant or dividing. We just need the DNA.'

The cartridge also covers other indications, e.g. diabetic foot, surgical site, deep skin and tissue infections as well as cardiac and catheter-related infections. The i60 cartridge was launched in May 2014 after thorough testing in a CE performance evaluation study comprising about 800 native analytical and clinical samples such as swabs, synovial and sonication fluids, tissue and catheter tips.

'Among others, our cartridge detected several key pathogens with sensitivities in the range between 75 to 100 percent at an overall panel sensitivity of 67 percent and panel specificity of 97.8 percent for the 81 analytes that have been successfully validated so far,' Schacht added. 'We also identified about 150 clinically important pathogens not found by standard microbiology culture. In particular, in every second sonication fluid and every third synovial fluid sample, i60 detected pathogens missed by microbiology culture.'

The cartridge is now in clinical evaluations in more than 20 hospitals across Europe and is also being evaluated in the investigator-initiated European Prosthetic Joint Infection Cohort Study (EPJIC). The EPJIC started in autumn 2014 and will enrol up to 5,000 PJI patients from up to 100 study centres across Europe. As part of the study, 500 patient samples will be measured by the Unyvero i60 ITI multiplex PCR cartridge system to identify pathogens involved in prosthetic joint infection.

'Adding rapid molecular testing to today's standard of care bears great improvement potential for patients, as well as hospitals and their health economics,' said Dr Andrej

The Unyvero i60 ITI multiplex PCR cartridge system is able to identify pathogens involved in prosthetic joint infection.

EU: Connecting laboratory medicine

‘Kissed by Europe’

They are not such strange bedfellows, say Walter Depner (Frankfurt) and Professor Norbert Gässler (Hildesheim), who find themselves ‘kissed by the European lab muse’ and were prompted to ask: What links literature and laboratory medicine at a European level?

Commentary: Walter Depner, Prof. Norbert Gässler

Norbert Gässler, from the Medical University in Hanover

Walter Depner, Lab Consulting, Frankfurt/Main

A few days after the German Conference for Laboratory Medicine (DKLM) closed its doors in Mannheim (27 September), just a few miles further north the Frankfurt Book Fair began (8 October). At the largest annual gathering worldwide of the literary industry the winners of this year’s European Union Prize for Literature were introduced by Danish author Janne Teller, who said, ‘Dear world, kiss a European, they need it; dear Europe, kiss the world, you need it.’

‘What does it feel like to be kissed by Europe? The best way to find out is to read European literature.’

By now, the clever visitors of many medical events – and EH readers – will have substituted the word ‘literature’ with ‘medicine or ‘diagnostics’; and strangely enough, they will feel the same sense of urgency, the same issues that need to be addressed. When Janne Teller asks, ‘How can Europe turn from a bureaucratic maze into a literary adventure’, we can relate very well to the bureaucratic maze and look for the ‘medical consensus’ rather than for the literary adventure.

Given Janne Teller’s question as to whether literature can help relieve the tensions within Europe, we can ask what can or should medicine do to relieve European tensions in healthcare.

Just like Ms Teller, we can also ask what Albania and Great Britain have in common, with regard to medicine rather than literature. To make the long European story short: Struggling with Europe is not something only novelists or physicians do. It appears to be a rather widespread condition across many professions. Indeed, DKLM, the German professional association of scientists in laboratory diagnostics, offered a European overview of the emerging components of the profession ‘bioscientist’.

BNLD chairman Dr Jürgen Hallbach provided a summary of the tasks bioscientists take on in the European healthcare systems, focusing on the Netherlands, Switzerland, the United Kingdom and Germany.

In the Netherlands the Nederlandse Vereniging voor Klinische Chemie en Laboratoriumgeneeskunde (NVKC) was founded in 1947. Its members are physicians and clinical chemists, the latter being mostly lab managers. Registration is required and has to be renewed every five years, but the profession is not officially recognised.

In Switzerland, in an attempt to harmonise training, the Swiss Academy for Medical Sciences (SAMW) introduced a five-year interdisciplinary continuing education programme in laboratory medical analytics, which encompasses haematology, clinical chemistry and immunology, medical microbiology and genetic lab analytics. The programme is geared towards physicians, pharmacists, chemists, biochemists, microbiologists and biologists. Graduates of the programme are specialists for clinical chemical analytics and, as such, are certified to manage a lab, including invoicing.

Nevertheless lab managers in university and large non-university hospitals are primarily clinical pathologists. Particularly between 2009 and 2013 a significant influx of German clinical pathologists was recorded. In short, while Switzerland does offer advanced interdisciplinary training for scientists and physicians, physicians fill most lab manager positions.

In the UK, physicians and scientists work in the field of laboratory medicine. Registered with the Health & Care Professions Council (HCPC) as non-medical professionals, they are called Clinical Scientists or Biomedical Scientists. The title is legally recognised and protected. The Association of Clinical Biochemistry (ACB), which was founded in 1953, registers these specialists and organises the continuing professional development.

In Germany, specialists with different backgrounds go into lab medicine. On the one hand there are medical-technical laboratory assistants (MTLA), non-academic professionals who must be under the constant supervision of specialist physicians and clinical chemists. On the other hand, there are specialist physicians in lab medicine and clinical chemists. Physicians who graduated from medical school can join a five-year specialist physician-training programme in lab medicine. They have to acquire 250 advanced training points and research activities are recommended. The State Medical Association awards the officially recognised degree.

Bioscientists can obtain a certificate as clinical chemists following their university degree. The five-year programme is designed by the Deutsche Vereinte Gesellschaft für Klinische Chemie und Laboratoriumsmedizin (DGKL), which also conducts the examination and issues the non-officially recognised certificates. Certificate holders – clinical chemists – are allowed to manage a lab, but are not allowed to invoice services.

To be able to distribute human resources and expertise in laboratory medicine more evenly across the European Union and to facilitate mobility, initial and advanced training as well as the official recognition of degrees and occupational titles need to be harmonised.

Within the EU the European Union of Medical Specialists (UEMS) and the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) represent the interests of clinical chemists and lab medicine specialists, particularly with regard to advanced training.

The main task of UEMS is to harmonise the job description so that lab medicine specialists can work throughout Europe. The organisation developed a syllabus defining the advanced training contents for both scientists (clinical chemists) and physicians (lab physicians).

EFLM is the European chapter of the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), i.e. it represents the scientific societies of all clinical chemists and lab medicine specialists in Europe. EFLM also developed an advanced training syllabus that is, to a large extent, identical with the UEMS syllabus. Graduates of the programme are registered in the so-called EC4 register and hold a certificate and also carry the title European Specialist in Laboratory Medicine. The certificate is valid for five years and can be renewed upon presentation of 250 continuing education points.

Europe-wide, there are about 30,000 lab medicine specialists, two thirds with a science or pharmacy background, a third with a medical background.

Targeted harmonisation of post-graduate training in lab medicine is a major challenge – be it on a national level, be it for the national professional associations of clinical chemists and lab medicine or clinical disciplines. No doubt it requires constructive collaboration of all lab medicine societies in all EU countries.

Moreover, harmonisation must not compromise the quality of care and the quality of research. It is the task of all actors in our discipline to get actively involved in finding solutions to these challenges.

For us, Janne Teller’s question can be rephrased: ‘How can Europe find its way out of the bureaucratic maze and move towards a medical consensus?’

Oliver Schacht, CEO of Curetis AG, which has developed a highly multiplexed, PCR-based lab-in-a-cartridge for fast automated diagnosis of pathogens

Trampuz, Professor at Berlin’s Charité Medical University and an EPJIC initiator. Trampuz added that Charité has already developed a new treatment scheme, which, based on exact and early diagnosis, allows a better-informed selection of surgery procedures in PJI patients. The success rate of the novel scheme – based on remissions – is 95 percent compared to 68 percent for the standard treatment scheme.

Informed decisions thereby not only offer potentially significant cost savings but also of avoiding worst-case scenarios of patients with severe, multi-pathogen infections that are multi-drug resistant and can incur costs for the hospital of several hundred thousand euros per patient.

Introducing stain-free 3-D digital pathology

Biopsy results while you wait

Gideon Ho, CEO and co-founder of Singapore-based HistoIndex is confident: 'After a biopsy a patient waits in a hospital bed, but now, instead of waiting a couple days until doctors know how to treat this patient, we can deliver results while the patient is still in the hospital.' This is because the firm has developed a laser-based, multiphoton imaging system for tissue diagnosis that eliminates the time-consuming process of sample staining. 'It's phenomenal,' he added, 'a paradigm change that will disrupt many things.'

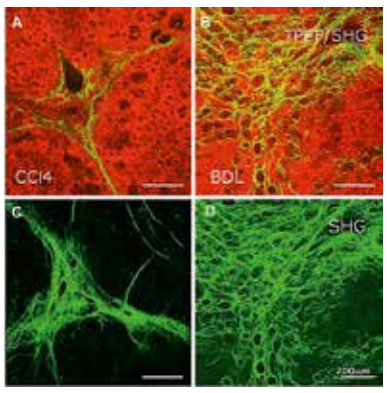
For pathologists who use traditional light microscopes, staining tissue samples is essential because it provides a contrast that can spotlight cellular features, such as tumours.

Eliminating time and costs for staining slide samples alone could revolutionise lab analytics. However, like a smart phone, the compact desktop Genesis200 instrument from HistoIndex is loaded with capabilities that accelerate the workflow, enhance diagnostic quality, and ultimately benefit patients.

After loading a biological specimen on the Genesis instrument the operation is fully automated from scanning to image processing and even analysis.

The technology at the heart of the Genesis platform is two-photon excitation fluorescence (TPEM) using a femtosecond laser that results in the emission of a photon that passes through a crystal and then a prism to generate a second-harmonic wave.

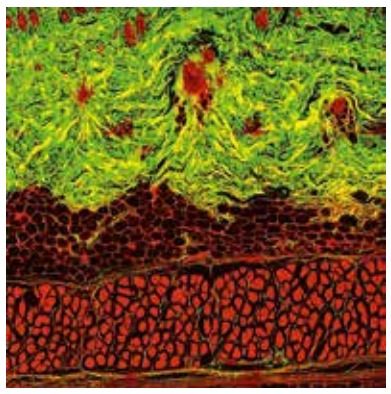
The non-linear, dual-channel imaging technique results in a high-resolution image that maps tissue samples and enables fine measurements in three dimensions.



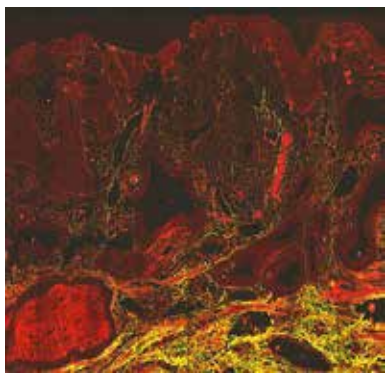
Rat model fibrosis study, with images taken from Carbon tetrachloride (CCl4) and Bile Duct Ligation (BDL) using Multiphoton Microscopy.
A) and B) are images obtained from Two Photon Excited Fluorescence (TPEF) together with Second Harmonic Generation (SHG) from CCl4 and BDL, respectively. C) and D) are the corresponding 3-D projections of 50-um-thick tissue samples in the SHG channel only.
We can clearly observe the differences between these two models. In the CCl4 model, collagen fibers (green) aggregated around vessel walls as liver fibrosis progressed, whereas fine collagen fibers distributed in sinusoidal areas disappeared. In the BDL model, collagen fibers aggregation took place around vessel walls, as well as in areas where bile ducts proliferated. Hepatocytes (red) are shown in the TPEF channel

This 3-D visualisation of bulk samples represents another revolution for tissue diagnosis enabling an examination of morphology to a depth of 300 micrometres, features that are usually lost when samples are thinly sliced for microscope slide preparation.

The digital capture also enables computerised assistance for quantification, eliminating inter- and intra-observer inconsistency.



Visible morphological features of rat skin cross section. We can observe normal rat skin – with no disease and clearly distinguish dermis, adipose tissue, connective tissue, skeletal muscle, and follicles, together with the collagen content



Effective application of Genesis200 Imaging system based on Two Photon Excited Fluorescence (TPEF) and Second Harmonic Generation (SHG) in the study of Cervical Intraepithelial Neoplasia (CIN) in mice. The two-layered structures of cervical tissue from the mice enable us to visualise the two-layered cervical microstructures, monitoring the metabolic activity and the density of epithelial cells as well as giving the ability to measure the epithelial cell nuclei size, together with the thickness of the epithelial layer and quantifying collagen in the stroma

Uploading data sets to the cloud brings the full power of the digital revolution to tissue diagnostics creating the possibility to share and compare results.

'Everything goes up to the cloud and connecting, bringing us closer to integrated diagnostics, the potential for combining test results for a fuller -omic view of the patient – using proteomics, in our case, with next-generation genomic sequencing,' said Ho.

The Genesis200 is approved for commercialisation with a CE mark, though the strategic focus is on research centres rather than high-throughput labs.

Gideon Ho gained his Master Degree in Engineering (M.Eng.) at the School of Mechanical and Production Engineering, Nanyang Technological University, in 2000. He finished his Doctorate in Philosophy (Ph.D.) in the Bioengineering Unit of the University of Strathclyde, Glasgow in 2004. His research topic was low-level laser therapy on tissue-engineered skin substitutes. In August 2010 he co-founded HistoIndex Pte. Ltd, of which he is CEO. His job scope includes commercial strategy, development of the company and aligning all functions of the company to meet its strategic commercial objectives. He also has a Certificate in Strategic Leadership of Technology and Innovation from Stanford University Graduate School of Business.

Grading of human breast cancer biopsy tissue samples based on Second Harmonic Generation (SHG) and Two Photon Excited Fluorescence (TPEF) with visible discrimination of the different collagen types (in blue & green)
(Results obtained with a new Polarisation feature of Genesis200)

Full commercialisation of the technology will come in 2015 with a new instrument, the Laennec, combined with the FibroIndex software and connecting to the Liver Cloud.

The Laennec analyser is currently in the regulatory approval process 'everywhere,' said Ho.

Follow-on products for the Genesis platform will see the introduction of multi-modular, multi-organ imaging capabilities to expand the HistoIndex footprint in the lab for tissue analysis.

'Who can remember how we worked without smart phones? Digital pathology is going to bring the same revolution to clinical diagnosis with smart instruments and we are at the centre of what is going to happen,' Gideon Ho said, with confidence.

CE Marked Genesis200 Imaging system from HistoIndex

Images: HistoIndex

Santa's

We are seeing great priority shifts in China's funding for R&D and manufacturing expansion. Even the agency responsible for selecting the recipients has changed, Jie Ren reports from the Beijing-based market analysis consultancy Whitney Research Inc.

Under which tree will Santa Claus leave a gift? To develop Chinese manufacturing capabilities the Ministry of Science and Technologies, since the mid-80s, has awarded grants from the National '863' programme. In the past decade medical devices, and particularly in vitro diagnostics (IVD), gained very large grants for R&D and to expand production.

Initially, products were mostly copies of multinational automated chemistry analysers and immunoassay analysers, with perhaps hundreds of domestic companies introducing automated chemistry analysers – although not too competitive in the high-end large city hospitals; mostly they competed with other Chinese firms in second tier cities and lower class hospitals with few patients and samples. They could not replace imports – despite huge expenditure.

Asked why it was suddenly introducing automated chemistry analysers, one firm replied that the market was hot for them. 'It must be,' it explained, 'look at all the companies getting into it.' China's scientific market research is still not very scientific.

Into which Christmas stocking will molecular fit?

Molecular is a newly focused phenomenon. In China, PCR (Polymerase chain reaction) was first clinically introduced in the '90s, but a lack of skilled labour and lax regulations brought many false positive results – primarily from contamination. The Ministry of Health banned the clinical use of PCR and, in 2002, released strict clinical PCR lab regulations: clinical PCR labs and technicians were to be Ministry of Health certified. As of April 2014, about 1,800 certified clinical PCR labs nationwide have reported clinical results – from multinational and Chinese equipment and reagents – reaching reasonable standards.

Despite heavy regulations, lag time for CFDA and for the Ministry to modernise alongside newer technologies, the still comparatively small molecular diagnostic market has experienced rapid growth. We expect well over 20% in the next several years, driven by healthcare reform, an aging population and improved test payment capabilities.

China's 12th five-year plan lists molecular diagnostics and companion diagnostics as significant development projects, and will establish 30-50 clinical translational medicine centres nationwide, and build 30-40 bio-pharmaceutical development and industrialisation bases for antibody, vaccine and diagnostic reagents development, as well as cultivate 10 leading enterprises.

Today, PCR-based diagnostic products still dominate China's molecular market, of which infectious disease tests, particularly HBV and HPV are primary products. Most domestic manufacturers focus on PCR tests using established technologies.

HIV and HBV molecular tests are now required for blood screening. ELISA, widely used for these, showed lower sensitivity. Promoting a nucleic acid test for blood screening, the National Health and Family Planning Commission aims to have 100% nucleic acid tests in Beijing and Shanghai,

bag full of cash for R&D

80% in east China, 70% in middle China, and 60% in West China, all by 2015. Blood screening test reagents are registered in the CFDA drug department, with very strict requirements. Thus the blood screening nucleic acid test market has few players, including Roche, Novartis (Chiron), Shanghai Haoyuan, Kehua, and Daan. Gene sequencing, with major clinical use in prenatal testing, In 3-5 years, the net manufacturers' revenue from prenatal tests will be around $600-700 million annually. Gene sequencing for cancer and genetic disorders is also accelerating. Companion diagnostic tests have already seen rapid growth, according to our interviews with lab leaders in Class III hospitals.

Molecular diagnostics requires skilled professionals and expensive instruments, which limits their market in lower level hospitals. Cost effective, easy to operate point of care (POC) products will expand the lower level market for molecular diagnostics, as well as show up in satellite and specialist labs.

More molecular automation and integrated instruments are the future trends for large labs but the number of healthcare institutions outside large city hospitals increases exponentially. Again, many foreign companies are collaborating with Chinese firms to take full advantage of the market.

Enigma Diagnostics, with a very impressive molecular POC offering, has teamed with the reagent firm Leadsman to enter the market from which Cepheid has out-priced itself. UStar, which we identified as a top prospect to the Gates Foundation and FIND (Foundation for New Innovative Diagnostics) in Geneva, has an interesting technology for molecular POCT and is now directly invested in by Gates and Lenovo to broaden the UStar product portfolio.

Many interesting developments in molecular POCT are progressing, primarily with overseas Chinese financially supported to bring innovation to Chinese firms. These innovative molecular diagnostic companies are the new darlings of the Chinese funding programmes as well as independent foreign investors.

Overall, the molecular diagnostic market is very lucrative in China. Nonetheless, some obstacles still exist – registration possibly among the first. All class II and class III products not on the exemption list must do clinical trials in China. The China Food and Drug Administration (CFDA) rules require imported products to be registered in their home countries before applying for CFDA approval.

Therefore, joint venture and collaboration with domestic companies has been a way to expedite Chinese market entry. Both Illumine and Life Technologies recently chose to expand their China gene sequencing market through local partnerships.

After 20 years of PCR, gene sequencing faces a similar situation in China. Beginning in 2011 with prenatal testing, early this year the CFDA and National Health and Family Planning Commission (now including the former Ministry of Health) banned clinical use of gene sequencing, but requested applications for an experimental centre and began to take applications to register products one month later. To date, no experimental centre has been approved and only BGI received CFDA approval, in a quite speedy fashion, for gene sequencing for clinical diagnostic purposes. Daan received their sequencing approval in November 2014. Several other gene sequencing companies have applied. Foreign gene sequencing products must first be approved in their home country and only Illumina, which approached China by collaborating with local firms, has received home country approval.

The Health and Family Planning Commission is encouraging class III hospitals to purchase domestic medical instruments, empowering the country's Association of Medical Instruments to select high quality, competitive domestic medical instruments and reagents – finally creating a catalogue and evaluation system as a purchasing reference.

This started with X-ray and ultrasound machines and biochemistry analysers. Selection standards include 60% technical performance, 20% professional opinions and 20% company performance, plus company size, sales volumes, market share, financial condition and service. This policy may also increase merger and joint ventures between foreign companies and domestic companies.

We think we see a shift in the government monetary awards to manufacturers, in keeping with other reforms that President Xi has prioritised. If followed, grants will no longer go to mediocre establishments with 'relationships', but will be based on real innovation and technological merit. Collaborating with foreign companies will be encouraged – so, as a prospective grantee or grantee partner, you'd better watch out. Just being mediocre will not make it. Just be 'good', for goodness sake.

Jie Ren received a master's degree in Cell and Molecular Biology from Fordham University in New York and a Masters in Veterinary Infectious Diseases in China. At Whitney Research she focuses on the molecular testing market.

Only the stepchildren in diagnostics and therapy – ***Part 1***

Iron deficiency and anaemia

Iron deficiency and resulting anaemia cause fatal comorbidities worldwide. Despite this, they are generally underestimated. Professor Lothar Thomas, specialist in laboratory medicine at Central Laboratory of the University Hospital of Frankfurt/Main, is calling for more information about the new laboratory parameters for diagnosis and monitoring of iron deficiency and iron substitution therapy. Dr Wolfgang Hildebrandt, of Siemens Healthcare Diagnostics GmbH, interviewed him about recent options in laboratory diagnostics.

Lothar Thomas, specialist in laboratory medicine at the Central Laboratory, Frankfurt/Main University Hospital, Germany

The average prevalence of iron deficiency in Europe is five to 10 percent.* Whilst diagnosed in 4-8% of children between 13-15 years of age – at 20% – the highest prevalence is seen in women during their reproductive years.

However, what no one ever says publicly is that iron deficiency also occurs often as a fatal comorbidity in chronic illnesses, such as kidney disease and renal insufficiency, chronic heart failure, intestinal diseases, obesity and tumours, as well as tumour treatment.

Why aren't clinicians and public health groups more aware of iron deficiency and its seriousness?

Lothar Thomas: 'One reason is that, despite its detailed knowledge and innovative laboratory diagnostics about iron deficiency and anaemia caused by iron deficiency, laboratory medicine has been unable to educate clinicians in a convincing way for the past decade. This partly has to do with the clinical acceptance of laboratory medicine, which varies significantly in Germany. In daily clinical routine, the laboratory is often seen as a service provider and less so as a competent, equal partner. Therefore, the laboratory is little consulted in the establishment and correction of disease-related clinical guidelines on diagnostics and therapy.

'Perhaps some of the innovative laboratory parameters or diagnostic algorithms are too complex to understand and interpret and therefore may be too complicated for the users. We must find new ways to convey our expertise and diagnostics in a practical way.'

Iron is generally a component of plant and animal food sources. The average daily need is only one or two mg, and the daily diet of central Europeans, with 15 mg to 20 mg, contains an excess of iron from food – so why are there iron deficiencies?

'The causes for iron deficiency vary. First, it can be differentiated by events such as blood loss due to menstruation, blood donation, trauma, chronic inflammatory diseases and tumours. Secondly, there are situations with increased requirements, e.g. pregnancy, growth and high-performance sport and thirdly, the limited uptake through e.g. malnutrition, stomach, intestinal problems and inflammations.

Fig. 1: Causes for Iron Deficiency

Category	Causes
Blood loss	Trauma, surgeries, blood donation, birth, menstruation, chronic bleeding (intestinal tract), cancer
Chronic diseases	Chronic heart failure (CHF), chronic inflammatory intestinal diseases (Crohn's disease, ulcerated colitis), renal deficiencies, rheumatoid types of diseases, inflammations and infections, obesity, cancer (cancer required chemotherapy)
Increased iron requirement	Pregnancy, high-performance sport (particularly women), growth phase (children and teenagers)
Malabsorption	Stomach and intestinal surgeries, duodenal malabsorption (celiac disease, diarrhoea)
Nutrition	1. Malnutrition, diet (junk food: high in calories, little trace elements)
	2. Unfavourable dietary composition: – Less meat (heme iron), more nutrients low in iron – Chronic alcohol consumption – Too high concentrations of iron absorption inhibitors: – Polyphenols (tannin in black tea, chlorogenic acid in coffee) – Phytic acid in unfermented whole grain cereals – Some proteins from soy, milk and egg white – Oxalate (spinach, rhubarb), salicylate (Aspirin) – Phosphate (meat, cheese, additives)
	3. Lack of vitamins such as vitamin C, folic acid, vitamin B12
	4. Milk replacement products based on cow milk for infants that are not enriched with iron
	5. Insufficient iron consumption in men and women over the age of 80

© Siemens Healthcare Diagnostics 2013.

'To illustrate this: menstruating women lose 50 mL to 60 mL of blood and therefore 25 mg to 30 mg of iron, which must be compensated. With 500 mL of blood loss, a blood donor has instantly 250 mg less iron. Usually, such an acute loss can be balanced by the stored iron of the body's own reticuloendothelial system bound to ferritin (500 mg iron in women and 1,000 mg iron in men).

'Subsequently, the iron storage must be quickly replenished. 'However, our body can only absorb a small portion of the need-dependent orally added iron. If we take 10 mg of dietary iron, up to six mg of it can be absorbed. However, we only absorb 15 mg of 100 mg of dietary iron, i.e. the absorbed quantity is less the more dietary iron is offered.'

Is there a difference between iron consumed in meat or plants?

'It must be clearly stated that the heme iron from meat products – particularly "dark" meat – is significantly better absorbed than iron from food of plant origin. Women, who generally consume more vegetables and fruit than men, and particularly vegetarians are at a significant disadvantage. Only 10 percent of the iron content from plant sources is absorbed; so it's not easy to balance any deficiencies with standard nutrition.

'Therefore it can be concluded that iron requirement and iron supply are in an instable balance. After all, the German Society for Nutrition recommends men take 10 mg and women 15 mg of iron per day through their diet. However, in this context, it is important to have a sufficient quantity of vitamin C in the diet because enteral iron absorption is ascorbic acid dependent. Ingredients in coffee or tea immediately after a meal have a counterproductive effect.

When does iron deficiency become complicated?

'Iron deficiency without anaemia is found three times more often than iron deficiency with anaemia. For as long as the iron deficiency has not developed into anaemia, we speak of an uncomplicated iron deficiency. However, it must always be understood as a precursor to anaemia.

'Problems arise, if the stored iron has already been depleted, or has not been adequately replaced or, in the event of increased requirements, the storage iron cannot be mobilised e.g. after stimulation with recombinant human erythropoietin (rHuEPO).

'We have this situation in inflammations with CRP levels of >5 mg/L. This is caused by the polypeptide hepcidin formed in the liver, which is the central regulator or iron homoeostasis.

'Under normal circumstances, an increase in this protein regulates the iron metabolism by slowing down iron absorption from the intestine, the iron transport to the placenta and the re-release of recycling iron from the reticuloendothelial system. On the other hand, if the iron requirement increases, the hepcidin level is regulated downward.

'In chronic inflammations, the inflammation promoting interleukin-6 also leads to an increase in hepcidin level, which in the end leads to an anaemia caused by inflammation through this causes permanent blockade of iron release from the macrophages, which decompose old erythrocytes in the spleen.

'Serious iron deficiencies are then expressed as microcytic hypochromic anaemia. Therefore, it is important to recognise any iron deficiency in the early phase, prior to the development of anaemia.'

What are the signs and effects of iron deficiency?

'There are many symptoms of iron deficiency. First, it should be determined when such symptoms occur. We differentiate between three stages: the storage iron deficiency (→ iron supply), the iron deficient erythropoiesis (→ iron requirement) and the iron deficiency anaemia.

'If the iron deposits are empty due to a negative iron balance, but the functional iron is not yet affected in its circulation, then there are no clinical symptoms of iron deficiency. If the iron deposits are depleted and less functional iron is now circulated, then it leads to an insufficient iron supply, the erythropoiesis.

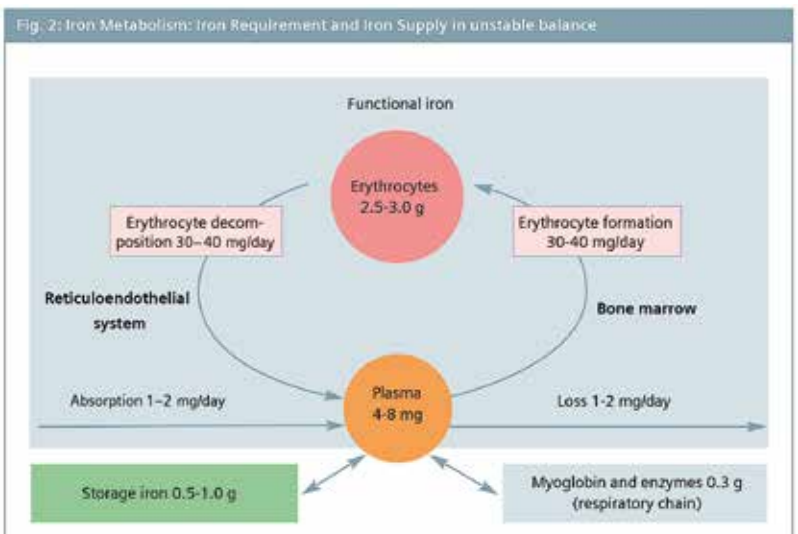
'The iron-dependent cell functions of the organisms (such as the iron-dependent enzyme of the respiratory chain) are just as affected. In this sub-clinical condition, we don't see any anaemia; however, there can already be physical signs of discomfort.

'If the result is anaemia because the iron is not substituted, then the problems escalate. Often, patients only seek medical advice when they suffer severe discomfort, i.e. during the later progression of the sub-clinical and functional iron deficiency, or even after the iron deficiency anaemia has manifested itself. Patients feel tired and are running on a low "energetic flame". Their quality of life is impaired. Particularly in children there is the risk of growth disorders due to severe chronic iron deficiency and neurological as well as cognitive losses can develop. These cannot be revised. Iron deficiency symptoms are expressed in many ways and it shows multiple symptoms.'

Part 2... To be continued in EH in 2015

* Source: The German Society for Haematology and Medical Oncology

Fig. 2: Iron Metabolism: Iron Requirement and Iron Supply in unstable balance

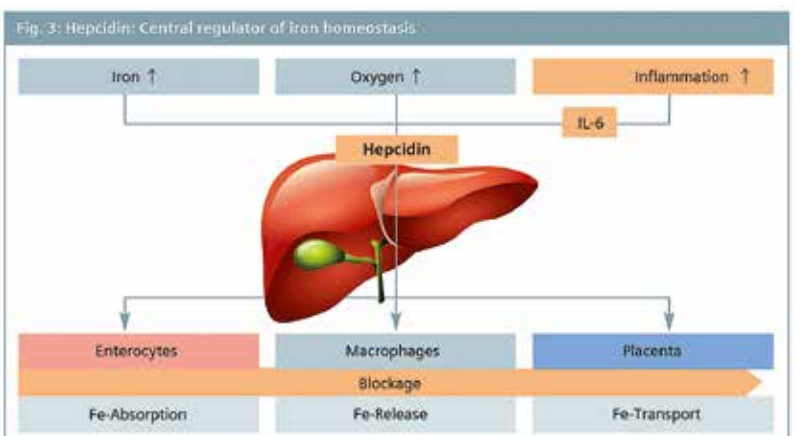


The iron level of adults is approx. 3 - 4 g (in men more, in women less) and it consists of three components:

Functional iron	Heme-bound iron (haemoglobin 2,5 g, Myoglobin und Enzyme 0,3 g)
Transport iron	In the blood bound to transferrin (20 - 30% saturation)
Storage iron	RES, hepatocytes, bound to apoferritin, ferritin and hemosiderin

Grafik modified acc. to: Thomas, L 2005, Dt. Ärzteblatt Jg. 102 Issue 9, 580587. © Siemens Healthcare Diagnostics 2013.

Fig. 3: Hepcidin: Central regulator of iron homeostasis



Increased hepcidin (hepatic bactericidal protein) levels are the cause for ACD (Anaemia of chronic diseases).

© Siemens Healthcare Diagnostics 2013.

Fig. 4: Symptoms of iron deficiency with multifarious appearance

Category	Symptoms
Skin	Paleness of the conjunctivae, paleness of skin, hair loss, brittle nails, rhagades of the corners of the mouth, deformity of fingers and toes, smooth atrophic tongue
Neuronal	Memory impairment, difficulty in concentration, cognitive deficits (Foetal period and early infant period), depression, headaches, tinnitus
Circulatory systems	Increased heart volume, tissue hypoxia, heart arrhythmia, palpitations and angina pectoris, rapid rise in pulse during physical exercise
General physical symptoms	Fatigue and loss of energy, sensitivity to cold, cold fingers and hands, sleep disorders, loss of libido
The bodies own defence mechanisms	Increased susceptibility for infections
Syndrome	CFS (Chronic-Fatigue-Syndrom), RLS (Restless-Leg-Syndrom), ADHS ((attention deficit/hyper activity syndrome)

© Siemens Healthcare Diagnostics 2013.

A new filtering device spreads through Europe

Recycling blood lost during major surgery

Report: Mark Nicholls

Sucking up blood spilt during a major surgical procedure, or drained from a heart-lung machine after surgery, the Hemosep cell concentration system has a blood bag that uses a chemical sponge technology and mechanical agitator to filter red and white blood cells and platelets through a plastic membrane so that they can then be returned to the patient by intravenous transfusion. A critical benefit is that a patient receives their own blood back rather than having donated blood.

In recent months the system's inventor Professor Terry Gourlay, from Strathclyde University, Glasgow, has seen significant implementation in hospitals across Europe and the UK. 'Hemosep is a machine that's a cell salvage device for use during a whole range of surgery,' he explained. 'It was designed for cardiothoracic surgery but now has an application for accident and emergency, vascular and orthopaedic, anywhere there's likely to be substantive blood loss.

'There are other technologies that do the same thing, but they are invariably fairly complex centrifuge devices. Hemosep's USP is in its simplicity and the fact it does not use centrifuge but a powerful high performance super absorber.'

The advanced membrane in Hemosep does not permit the blood cells, including the smallest cells – the platelets responsible for clotting – to pass into the super-absorber. Therefore, Hemosep gives the patient back all their cells – red and white cells and platelets – rather than only red cells returned by other devices.'

The device consists of the Hemosep bag, shaker unit, a blood collection bag to hold the processed blood, and the intra-operative pump, suction and blood reservoir

Hemosep has been in development at Strathclyde University since 2007 and on the market since 2012, following successful clinical trials that were led by Professor Serdar Gunaydin, Head of Cardiac Surgery at the University of Kirikkale Hospital in Ankara, Turkey, which saw the system receive the CE mark for Europe.

'The primary benefit for patients of this type of technology is that they are getting their own blood back, which reduces the need for donor transfusion and risk of transfusion reaction,' he pointed out. 'Another advantage is that they are not just getting red blood cells but all cells and that can have a positive impact on reducing bleeding. The early clinical study also demonstrated that Hemosep removed pro-inflammatory molecules.'

For clinicians, the device is simple to use with no specialist expertise required and, for a hospital and health system, it reduces the need for donor blood and associated complications.

The Hemosep device also occupies a small footprint and is easily portable.

Along with wider use across Europe and Asia, there are plans to introduce the system into Africa and Australasia via Brightwake Ltd, specialist in research and development, engineering, production and global marketing of products. A key factor in the partnership with Brightwake has been the company's knowledge of textiles and expertise to invent filters with microscopic meshes. These make Hemosep the only machine in the world capable of salvaging the tiny platelets that help blood to clot. The avoidance of post-operative complications and a reduced reliance on blood banks mean potentially huge savings for the National Health Service (NHS), estimated at over £10m a year.

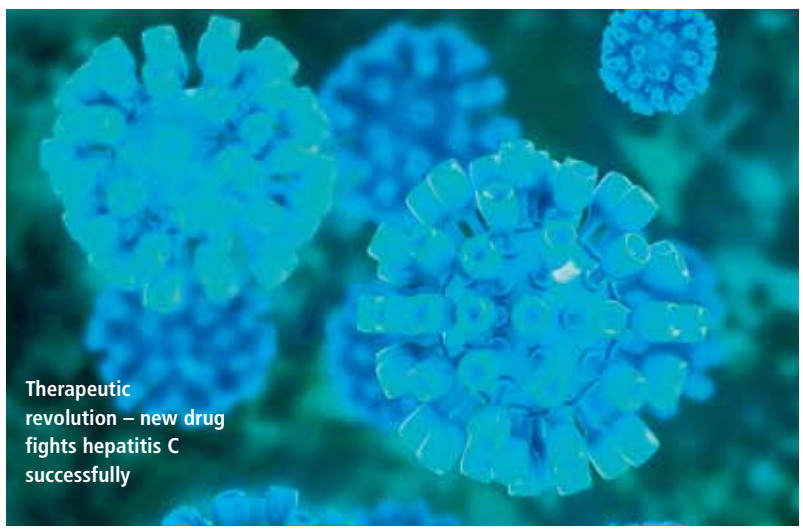
Next generation devices are already being developed as Professor Gourlay's team works with Brightwake to improve performance.

There are also adaptations planned for a military setting, where particular challenges include using it away from main centres, and for the development of a version that requires no power as well as a version for paediatric surgery and also veterinary surgery.

Terry Gourlay is Professor of Bio-engineering and head of the Department of Biomedical Engineering at Strathclyde University in Glasgow, Scotland. His main research interest is in cardiovascular devices with a specific focus on extra-corporeal systems, life support, ECMO, cardiopulmonary by-pass and implantable devices.

Breakthrough in hepatitis C research

Earlier this year a drug was launched that can cure hepatitis C without severe side effects in most patients. Whilst the treatment is fast, it is very expensive but does avoid liver cancer and thus makes liver transplants superfluous. This is only one of the many promising developments in hepatitis research that Dr Markus Cornberg of the Medical University Hanover has addressed at the Medica Education Conference.



Therapeutic revolution – new drug fights hepatitis C successfully

'Hepatitis C is a chronic infectious disease caused by a virus which was identified in 1989,' says Markus Cornberg, adding: 'Until recently the treatment consisted of a combination of interferon and ribavirin, two unspecific drugs of which we even to date don't know why they work.' However, only about 30 percent of the infected patients received the medication, the expert points out, since 'in patients hepatitis with advanced liver disease or other severe sequelae we could not use it due to the adverse effects.

However, now we have antiviral substances such as protease inhibitors, polymerase inhibitors and NS5A inhibitors which for the first time provide a targeted and effective hepatitis C treatment.'

The new drug can cure hepatitis C in more than 90 percent of patients with a course of treatment taking at most six months. 'The major advantage of these drugs is the fact that they have few side effects,' Cornberg explains. The drawback: They come with a price tag of up to 100,000 euros per course. 'The drug development costs have to be recovered but the price will drop,' Cornberg says but underlines that life-long therapies for other diseases are equally expensive.

In January 2014 sofosbuvir was introduced, simprevir followed suit in May and in August the third new drug, daclatasvir, was approved. In November, Gilead is expected to present an oral hepatitis medication that combines two of the agents and, for January 2015, AbbVie announced a triple combination.

In his presentation Dr Cornberg will also cover other forms of hepatitis, such as A and E. Both are prevalent in tropical countries, nevertheless Dr Cornberg explains that,hepatitis E pathogens can occur in Europe '...for example in food such as uncooked meat, ground pork sausage or wild boar meat.'

Approximately twenty percent of the German population are estimated to have been exposed to the hepatitis E virus, Cornberg says, but mostly with genotype 3, a rather benign variant, while in the tropical countries genotype 1 is common: 'In very rare cases we have patients with jaundice, albeit today we know that transplant patients or immunocompromised patients are particularly at risk.' They can develop chronic hepatitis, where the virus remains in the body and causes inflammations. 'Ever since we've understood this we detect the hepatitis E virus much more often. Before, we simply didn't look for it,' Cornberg explains.

In Germany, estimates mention up to one million carriers of hepatitis B and C with the major transmission vector for hepatitis B being sexual intercourse. Also in that coun, pregnant women are routinely tested for the virus to prevent a transmission from mother to the child. Most hepatitis B carriers do not show symptoms, 'the virus sleeps in the body and can break out at any time,' according to Dr Cornberg.

Immunosuppressant drugs such as rituximab are used to treat rheumatism, lymphoma or multiple sclerosis. But, Cornberg warns, the physicians should exercise prudence since these drugs weaken the antibodies, which in turn can activate the hepatitis B virus. The disease can be extremely severe, even fatal, Cornberg says and emphasises that physicians must be arware of this. Even in healthy patients who carry hepatitis B markers, rituximab can reactivate these markers. Then, a conventional hepatitis B treatment must be initiated. 'Unfortunately it does happen that patients are not properly tested before receiving medication,' he says, 'and then the liver function tests skyrocket and before it occurs to you that your patient might have hepatitis B, he's almost dead.'

Dr Markus Cornberg is managing senior physician at the Centre of Internal medicine as well as senior physician at the Clinic of Gastroenterology, Hepatology and Endocrinology at the Medical University, Hanover. His clinical work focuses on the treatment of patients with liver disease. He was lead physician in several clinical studies, which looked at new drugs for hepatic viral infections. In 2007 and 2010 he served on the organisational committee, which drafted the S3 guidelines for hepatitis B management.
His basic research focuses on the role of cellular immune responses with regard to the course of disease and the treatments response of patients with viral hepatitis.

Reimbursement rates must be negotiated

Last October the Association of the German Diagnostics Industry (VDGH) warned that the proposed EU regulation on in vitro diagnostic medical devices will increase production costs. Simultaneously with the Brussels proposal publication, the German Federal Ministry of Health presented a draft fees regulation that includes significant increases and several new fees, inter alia the minimum fee for the classification of medical products is set to rise from currently €200 to €1,400. EH correspondent Walter Depner interviewed Dr Martin Walger, Managing Director of VDGH in Berlin about the likely consequences of the new regulations.

Is it a coincidence that Brussels and Berlin presented draft regulations at the same time, or was this a planned action?

'The EU IVD draft regulation is – in some aspects massive – a tightening of current legislation that will cause significant cost increases for manufacturers. For a five-year product approval term, additional costs are estimated to amount to about €500 million Europe-wide. The industry, to be sure, supports the basic approach of the draft regulation, namely to enhance – within the existing legal framework – legal certainty and European harmonisation of laws in order to increase patient safety. 'We do support legislation, because we know that we need people to trust our products; but we as manufacturers also need to be sure we can trust the system of market access, market surveillance and market control. What we simply cannot support are measures that increase bureaucracy rather than safety.'

'The draft fees regulation by the German Ministry of Health proposes drastic fee increases and new fees. The extreme increase of the minimum fee is entirely unreasonable. The Ministry argued that classification decisions often involve complex review processes to determine whether a product is a medical, pharmaceutical or cosmetics product.

'The EU draft IVD regulation proposes a new classification system that will trigger more classification inquiries with the manufacturers. However, classification inquiries regarding an IVD product cannot be compared to those regarding complex medical or combination products.

'VDGH proposes to maintain the current fee of €200. A new fee of €160 is envisaged to report relevant incidents in connection with new IVD product tests. We consider the introduction of this new fee unjustified since law requires notification. Also, the majority of these notifications are not related to a specific product.

'During performance reviews, which run over a longer period of time, samples are taken intermittently. Incidents, however, do not occur when such samples are taken; incidents occur when study participants develop a disease. Even incidents that are not related to a product have to be reported. To charge a fee for this type of notification is, as far as we are concerned, an unjustified financial burden.

'On 10 November 2014 the adopted fee schedule was published. The minimum fee is €400 and the incident notification fee is between €25 and €250.

'The fee adjustments in German are not directly related to the EU IVD draft regulation, nonetheless they do create an additional financial burden on the IVD industry since, in the future, more classification decisions will have to be made.'

Why could the new classification system in the updated EU IVD regulation create an additional financial burden?

'Adjustments and cost increase, which are already contained in the regulation, are mainly caused by the new rule-based product classification, which complicates the approval procedure. In the future, a notified body will be involved in more than 90 percent of all in vitro diagnostic products. Notified bodies are test and certification bodies, which themselves are approved and controlled by the authorities. They certify quality management systems, review products and interpretations and release product batches. In order to prepare for the new EU IVD regulation and its effects a transition period of five years is required. This time is needed to manage the implementation of the new classification system, conformity evaluation processes and documentation requirements.'

Are there any Europe-wide estimates on the number of lab test approvals that will be concerned?

'The new classification system will apply to about 40,000 products of manufacturers throughout the EU; in Germany roughly 8,000 tests need to be classified. A small or medium-size enterprise, which has to reclassify about 100 products, cannot fulfil the requirements within three years.

'Additionally, after the adoption of the IVD regulation, both the European Commission and the national authorities will have to create certain preconditions, inter alia a European database has to be implemented and national law has to be adapted.

'VDGH does not oppose the new EU IVD regulation. However, we do demand that each new requirement is tested beforehand: does it really enhance patient safety or does it just inflate bureaucracy? The legislator has to take into account that in vitro diagnostic devices are never used in or with the human body. Consequently, their risk potential is, by definition, minimal. For manufacturers to be able to implement the new requirements, VDGH demands an adequate transition period. Earlier and comparable legal reforms granted five years.'

Why do you predict the future need for more staff?

'Two thirds of the companies affected anticipate that they need more staff due to the new classification system and the new approval procedure, which entails additional tests and documentation. Compliance with the new requirements cannot be realised with the current staff.'

It is anticipated that more lab tests will be categorised in higher risk classes. Do those classes mean higher approval fees and what is the range of minimum fees?

'A notified body will be involved in 35 to 40 percent of all conformity assessment procedures in risk classes C and D – currently the rate is about five to ten percent. For 90 percent of the products, the notified body will evaluate the quality management system. The manufacturers – in cooperation with the notified body – have to adapt their QMS and provide the necessary resources to make sure their products comply with the new requirements by the end of the transition period.

'We cannot yet calculate a precise figure regarding the additional costs. Per parameter, for what will be categorised in class C we expect additional costs to amount to €12,000 and €26,000; for class B parameter the estimate is €1,100 to €2,100. Approximately 30 to 50 percent of these costs will recur every year.'

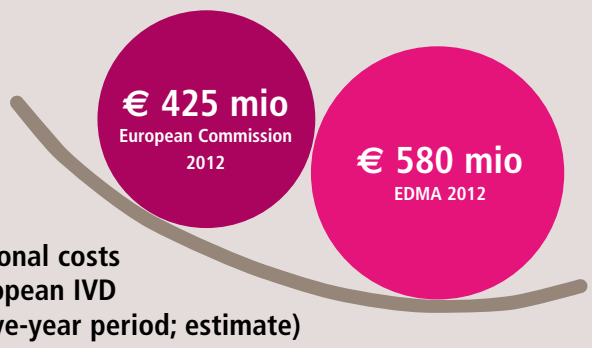
What significant problems might occur for the industry?

'Small and medium-size enterprises are the backbone of the German IVD industry: they account for 45 percent of the manufacturers, while less than nine percent are large corporations. The SME's financial capacities and their capacity to shoulder additional quantitative and qualitative requirements are fully exhausted. In a highly regulated market, such as lab services, costs cannot easily be passed on to the customer.

'The self-government bodies must take regulatory requirements into account when setting lab fees and they must negotiate economically viable reimbursement rates.'

Martin Walger manages the German Diagnostics Industry Association

EU draft IVD regulation
Repercussions for the manufacturers



Total additional costs for the European IVD industry (five-year period; estimate)

Sources: European Diagnostic Manufacturers Association (EDMA) 2012, European Commission 2012, VDGH member survey 12/2013

VDGH Verband der Diagnostica-Industrie