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POCT could lose economic attraction

Costs are often several times higher than those for core laboratory tests

Laboratory tests represent common, frequent and important decision support in patient care. Modern, rational healthcare would not be possible without an efficient laboratory service, warns *Dr Astrid Petersmann*


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In addition to physical examinations, medical history laboratory test results are critical in almost all medical decisions made in the hospital. The demand for adequate, fast measurements has increased exponentially over at least the last 50 years and may have increased 100-fold, or more, since the 1950s. This could not have been achieved without the introduction of partial or full automation, of course boosted by the availability of computers and micro devices.

Nowadays highly consolidated and complex analysers can run hundreds of different assays simultaneously at a rate of more than one thousand tests per hour. In the modernisation process monotonous, sometimes-dangerous work was eliminated and the precision and relevance of results improved beyond what was thought possible. This has been further emphasised by implementing quality management systems and formalised quality control mechanisms.

Laboratory medicine is responsible for only a comparatively small fraction of healthcare costs and amounts to less than five percent of these. However, the Point of Care Testing (POCT) market has grown much faster than the core laboratory market. Given today's efficient technology at hand in core laboratories, why has POCT also achieved an immense and accelerating growth in hospitals at the same time as core laboratories grew extremely efficient and highly standardised?

Costs for POCT reagents often exceed costs for core laboratory tests several fold. Investment costs for a single POCT assay systems may seem low but POCT devices are limited to one or few assays only and do not produce a fraction of results during their life cycle compared with instruments in the core laboratory. Additionally, the latter often handle hundreds of different assays. If investment costs were calculated per assay, POCT could lose its economic attraction. The investment costs may be hidden in the reagent costs when pay per use, or pay per patient result, are the basis for financing. Further, the price for a single assay POCT device may be affordable by individual hospital departments and the approval of hospital administration may not be needed. Managing directors might be surprised if they inspect their hospital for all POCTs in use.

Patient safety is a critical issue. In the same hospital, assays offered by the core laboratory and a POCT can be of high quality yet could still lead to discrepancies in results, especially if there is no centrally managed POCT concept. If a patient receives results from both systems during his stay this question will be raised: Which result is the correct one? How can the clinician deal with these discrepancies? What is common knowledge to Laboratory Medicine does not receive a high awareness in other professions among the hospital medical and administration staff: assays may differ systematically and it is not a rare finding, despite worldwide efforts for harmonisation.

An issue affecting economics and patient safety at the same time can be summarised as 'responsibilities connected to running laboratory test'. Regardless of how easy any POCT is, everyone in the workflow

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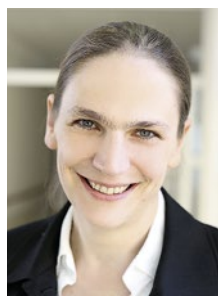

Biologist **Astrid Petersmann MD** specialises in laboratory medicine and is a senior physician at the Institute of Clinical Chemistry and Laboratory Medicine, University of Greifswald, Germany. She is also a member of the 'POCT' working group at The German Society for Clinical Chemistry and Laboratory Medicine (DGKL)

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POCT could lose economic attraction

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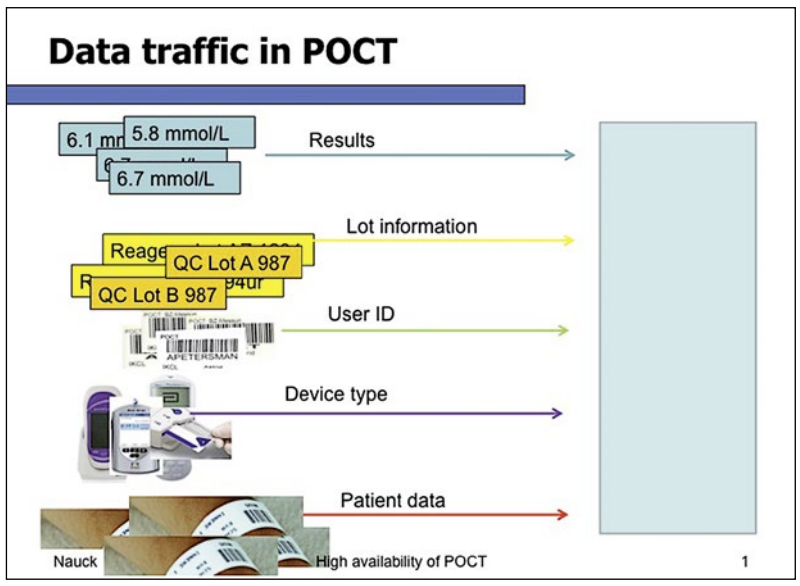

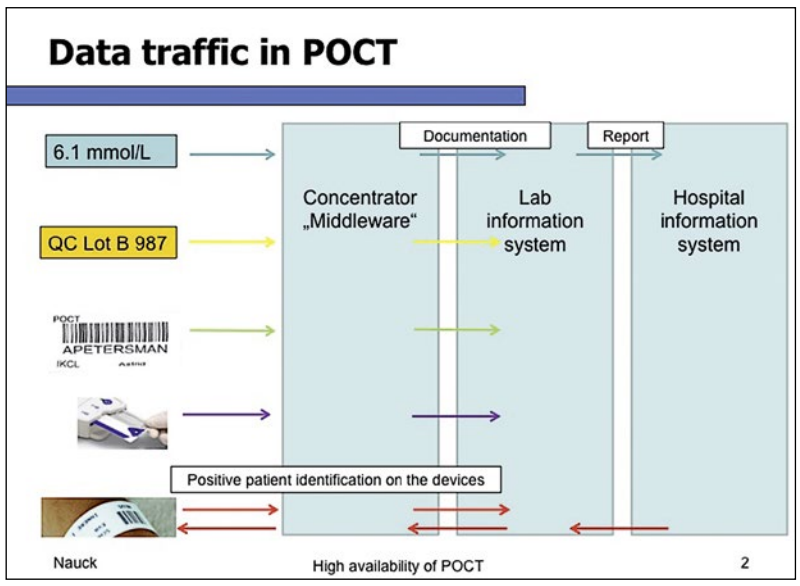

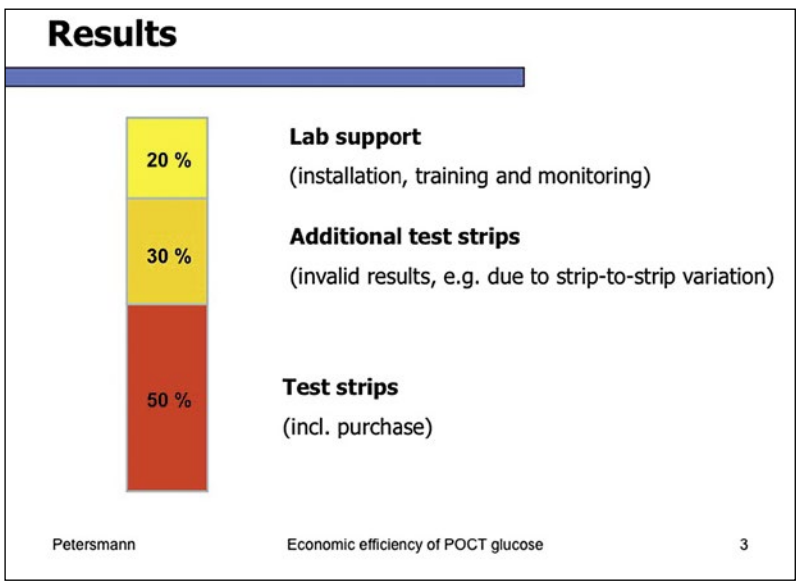

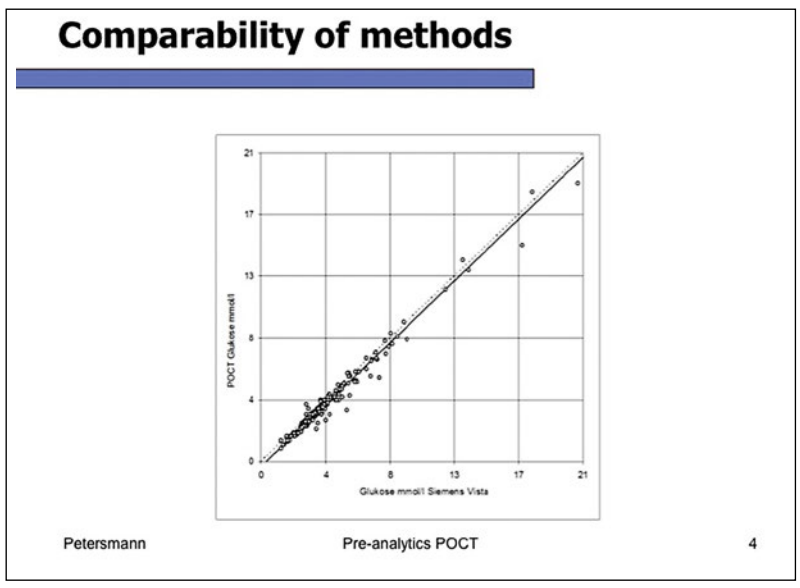

stages needs to be trained. One of the key features of POCT is the number of people involved.

Whereas a core laboratory has a rather limited number of staff, POCTs are often carried out by even thousands of hospital staff members across different healthcare professions. Even if training for one type of device takes a minimum amount of time, it immediately builds up huge demands of time and organising resources, if professionally done. Skills also need to be practised and maintained, or quality will falter. Regardless of whether a test result was obtained from a core laboratory, or a POCT, the same quality standards must be met. Therefore, there can be no compromises in quality assurance and quality management in POCT. Unfortunately, this is not always realised or practiced and imposes risks for patient safety. For instance, if connectivity to the hospital information system is missing, faulty instruments and reagents may be overlooked and create threats to patient safety. Also, the use of analytically poor devices, untrained or unlicensed users might lead to erroneous test results and errors in patient care. By the time thousands of users are involved, the risk of errors increases, bearing immense challenges for any quality management system.

Do the benefits of POCT exceed these risks for patient care and economic efforts? If properly used, certainly yes. Not without reason POCT has a long tradition in patient care. Measurements of blood glucose and blood gas analysis are well-known examples. One common key feature is their immediate impact on patient care that can hardly be achieved by the core laboratories. Even though a few hospitals manage to offer centralised blood gas analyses with the help of fast transport e.g. pneumatic tube systems, most hospitals operate blood gases as a POCT to meet urgent needs in intensive care. An immediately available glucose test result is often crucial in diabetic patients, when insulin dosage depends on it.

When it comes to hospital processes the issue becomes a little more complicated. POCT is thought to improve workflows by cutting short the time a test result from the core laboratory becomes available. Especially in emergency rooms this has become a trend that first focused on a few assays, such as Troponin. Nowadays, the assay menu offered in emergency rooms begins to broaden as suitable and consolidated multiple assay POCT instruments become available.

Some hospitals even create dedicated satellite labs in the emergency room equipped with POCT. If done professionally, this may be of considerable value for patient, hospital and staff. Still, the benefit of POCT on workflow, and consequently on costs, is controversially discussed. Even if theoretical scenarios for the positive impact of POCT on clinical workflows appear promising, sufficient and comprehensive studies are still missing. One reason may be that clinical workflows contain many steps and also depend on human beings. They can only be standardised to a certain extent, which is challenging for the evaluation of economic effects.

How then should POCT be used? Naturally, because both core laboratory tests and POCT are used for patient care in hospitals, they should have the same demands on quality standards. They are both subject to legal requirements, such as the EU-IVD and subsequently many other national and local regulations. To meet those standards POCT uses up more human resources than a core laboratory. These human resources are difficult to estimate and therefore often neglected in justifying a POCT solution. Neglecting the training efforts, maintenance, quality assurance and troubleshooting cost causes an enormous bias in economic considerations. The burden is often imposed upon health care professions, such as nurses or physicians who already are overloaded by tasks that are not directly experienced as related to their respective profession.

There are needs in patient care that can best be met by professionally and centrally managed POCT. Professional POCT management includes IT solutions that go hand in hand with the laboratory and hospital information system and also suitable instruments that fulfil analytical and workflow needs.

With all this in mind, POCT should be used as much as necessary and as little as possible. A point of care testing concept represents a key responsibility that should be interdisciplinarily developed and centrally decided in each hospital. ■

Immun strikin

Checkpoint inhibitors can achieve a lasting treatment response in around 20% of some kinds of advanced cancer cases

Report: Michael Krassnitzer

'Immunotherapies are given the highest possible rating on the Magnitude of Clinical Benefit Scale of the European Society for Medical Oncology (ESMO), which assesses the actual clinical benefit of tumour treatments,' emphasises Professor Christoph Zielinski MD, Head of the University Clinic for Internal Medicine I at the Medical University of Vienna and head of the Comprehensive Cancer Centre (CCC) in Vienna. 'We are on the brink of a revolution in treatment. The new concept is astonishingly logical as it is aimed at activating the immune system through switching off suppressive mechanisms against a tumour,' says the Viennese researcher who was involved in the development of immunotherapy for bronchial carcinoma, which is currently making international headlines. At a November event held by the CCC, Zielinski explained that new immunotherapies no longer only work on tumours long-associated with the immune system: 'In patients with advanced non-small-cell lung cancer, who had received extensive previous treatment, we have achieved a one-year survival rate of 42%, a two-year survival rate of 24% and a rate of 18% after three years through treatment with the monoclonal antibody Nivolumab.'

At Vienna's University Clinic for Dermatology the new generation of checkpoint inhibitors (Nivolumab and Pemprolizumab) have recently begun to be used as first line treatments. Various studies, in which the clinic has participated for almost a

New subspec hybrid imagi

In May 2015 the Executive Council of the European Society of Radiology (ESR) decided to establish a new subspecialty society, the European Society for Hybrid Medical Imaging (ESHI). Under ESR's umbrella, it will improve hybrid imaging training for practitioners to can make the best use of PET/CT and PET/MR. 'We hope this new society will help to stimulate a much closer collaborative relationship between radiology and nuclear medicine, and will provide a framework for future development of training, education and standards in hybrid imaging. It's very important that this unique field is represented by its own European body," said ESR President, Luis Donoso Bach, from Barcelona. .

The use of PET/CT and PET/MR is increasing alongside a growing need for knowledge/skills. In 2007, the ESR and European Association of Nuclear Medicine (EANM) published a white paper on multimodality imaging. In 2011, the multimodality imaging training curriculum, written by the ESR and EANM, was

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decade, have confirmed that seven to nine percent of all melanoma patients see a complete remission of their tumours. 'Many more patients experience at least a lasting remission,' emphasises melanoma specialist Professor Christoph Höller MD. 'This is remarkable given the bad prognosis for this disease overall.'

Buoyed by the success achieved so far, the Viennese scientists are continuing to work on improvements of this treatment. Höller: 'We are continuing to run studies on immunotherapy. We're researching the combination of the checkpoint inhibitors PD1 (Nivolumab) and CTLA4 (Ipilimumab). We are also starting a study where a PD-1 antibody will be combined with a genetically modified herpes virus.' The virus will be injected into the metastases and results in the disintegration of the tumour cells. The fragments of the tumour cells then provoke a strong, local immune reaction, which is further increased by the administration of the antibody. The basic principle of immunotherapy is to activate the patient's immune system and to direct it against the tumour cells. The so-called immune checkpoints play an important part here.

These are receptor proteins found on the surface of T-cells (white blood cells boosting immune defence). When specific signal substances (ligands) bind to the checkpoints the T-cells are slowed down. This mechanism serves the natural regulation of the immune system and prevents it from overshooting – as happens in the case of autoimmune diseases – and attacks the body's own, healthy cells.

However, tumour cells can also form ligands, which then inhibit the immune system via the checkpoints. If the checkpoints of the T-cells can be blocked, thus preventing the ligands from binding to the receptors, this activates the T-cells and triggers an immune reaction and combat against the tumour. This blockade occurs via the much-quoted checkpoint inhibitors, i.e. humanised monoclonal antibodies administered via infusion.

'For some types of advanced cancers treatment with checkpoint inhibitors can achieve a lasting response to treatment in around 20% of patients,' Zielinski stresses. New combination therapies are likely to significantly improve these results further still.

CCC/Photography Sabine Gruber

Christoph Zielinski MD is head of the Oncology Department and is Chairman of the Board at the University Clinic for Internal Medicine I, Medical University of Vienna, where he also heads the Comprehensive Cancer Centre, as well as the Vienna General Hospital. A specialist in internal medicine and oncology, he spent three years at the Cancer Research Centre of Tufts University, Boston. Today his research lies on breast and lung cancer, the clinical development of drugs, translational research, personalised medicine in oncology, and immunotherapy for cancerous diseases. With around 500 scientific publications to his name, and memberships in international medical societies, he is also President of the Central European Cooperative Oncology Group (CECOG) and a member (2014-2015) of the Executive Committee of the European Society for Medical Oncology (ESMO).

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published in 'Insights into Imaging'. This presents a knowledge base in multimodality imaging. In late 2014, a hybrid imaging training session was held at the Annual Leadership Meeting of the ESR's European member societies, and the majority of attendees supported the establishment of a European society for hybrid imaging. An ESR survey showed that radiology residents also want to increase nuclear medicine training. The ESHI will be launched at the European Congress of Radiology next March. Membership will be open to radiologists and nuclear medicine physicians.

In two decades USA analgesics prescriptions killed over 100,000 people

EU aims to avoid opioid epidemic

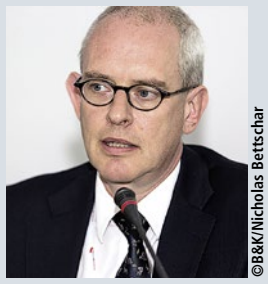
Anaesthesiologist, intensive care physician and pain expert Bart Morlion MD is president-elect of the European Pain Federation EFIC. He studied at the University of Leuven, Belgium, and completed a specialist residency at the Ruhr University, Bochum, Germany. He returned to Leuven in 1998 to become professor in the Department of Cardiovascular Sciences and head of the multidisciplinary pain centre. From 2006 until 2012 Morlion presided over the Belgian Pain Society and is the principal investigator in 28 national and international multicentre clinical trials (Phases II, III and IV).

In the USA, there is already talk of an 'opioid epidemic'. Whereas in the past 20 years some 100,000 people died directly or indirectly through prescribed opioids, reports indicate that more than 16,000 died in 2010 alone. Since the sales of opioid analgesics quadrupled between 1999 and 2010 recent debates have intensified surrounding the use of opioids for non-tumour-related pain in the USA, as well as Canada and Australia, with dependency and risks moving into the spotlight. The US Food and Drug Administration (FDA) restricted the indication for prescribing opioids and demanded that manufacturers conduct more studies on risks, such as abuse, addiction, excessive pain sensitivity, overdoses and fatalities.

This trend has reached Europe: The European Council has initiated a discussion of abuse and dependency on medications, with a focus on opioid analgesics.

European pain experts are worried about this development. Professor. Bart Morlion, president-elect of the European Pain Federation EFIC, warned those attending the 9th Congress of the European Pain Federation, in Vienna, against exaggerated caution; not to toss the baby out with the bathwater: 'Opioids provide important therapeutic options in bringing relief from acute and chronic pain. We should not re-stigmatise these analgesics, but instead clarify how they can be used safely and effectively.'

The professor is emphatically against generalising USA data and applying them to Europe. The abuse problem is virulent mainly in North America and Australia, since prescriptions are less regulated than in Europe, where access is strictly regulated by special prescription forms, or the addictive substances registry: 'Reports on increasing problems with opioids, particularly from North America, are mostly related to long-term prescription with a lack of careful patient selection and patient reassessment.' In some US states, so-called 'pill mills' – medical facilities that prescribe controlled substances without regard for guidelines and indicators – are allegedly responsible for numerous opioid-related fatalities. 'There are certainly many good reasons for the increase in prescription rates. However, in future more care needs to be taken to ensure that opioids are the right choice for the individual patient,' Prof. Morlion emphasises. 'Opioids are not without side effects. For this reason they should only be prescribed in cases where there is a good balance between pain relief and side effects, where there are long-term benefits, and where other methods of treatment have failed.'



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Professor Bart Morlion is head of the multidisciplinary pain centre at Leuven University, Belgium

It cannot be that abuse in some parts of the world leads to a global call for restrictions that could mean insurmountable hurdles for those urgently needing opioids for pain control.

Therefore, the European professional society seeks a reasonable approach between dramatic undersupply, over-prescription and the abuse problem. EFIC commissioned a working group to prepare Europe-wide recommendations for an appropriate and responsible handling of opioids, especially in long-term therapy of chronic pain. With recommendations expected this autumn, Prof. Morlion expects the '… guidelines should provide doctors throughout Europe with support and advice for optimal use of opioid analgesics that's easy to put into practice.'

UK hosp few post

Report: Mark Nicholls

Post mortems are now rarely carried out within UK hospitals – according to a study that examined all acute NHS Trusts within England, NHS Boards in Scotland and Wales and Social Care Trusts in Northern Ireland, and found that the process has disappeared completely in around a quarter (23%) of NHS trusts. In 2013, the average autopsy rate (percentage of adult in-patient deaths that undergo consented autopsy) in the UK was 0.7%.

'With the rapid rate of the decline, it will not be many years before this practice is extinct throughout the vast majority, if not all, of the UK,' suggests Angus Turnbull from Imperial College London, who led the research. 'This is the grave situation currently surrounding hospital autopsy. Thirty years ago, up to 28% of all in-patient adult deaths underwent consent autopsy.'

In the UK autopsy is divided into medico-legal autopsy – one required by law under the jurisdiction of a coroner – and consented autopsy, performed with the consent of the family of the deceased.

Effectiveness, safety and cost of fluorescence cystoscopy

Bladder cancer is associated with high recurrence rates, necessitating prolonged surveillance and repeated treatments. As a result, it is one of the most challenging and costly of all solid tumours to manage. Although most patients present at an early stage with non-muscle-invasive bladder cancer (NMIBC), between 13% and 61% will experience recurrence within 1 year of initial transurethral resection of the bladder (TURB). It is believed that many cases of recurrence may be due to incomplete initial resection caused by limited ability to visualise the whole extent of the tumour using the current standard, white-light cystoscopy (WLC). Improved detection and management are therefore urgently needed.

Fluorescence cystoscopy (FC) with photosensitive agents, such as hexaminolevulinate (HAL), has demonstrated enhanced ability to visualise malignant areas, including flat or multifocal lesions that are difficult to detect using WLC, thereby resulting in more complete resections and reduced recurrence rates. Many clinical trials, including registration trials, meta-analyses and systematic reviews confirm these benefits of HAL-FC as an adjunct to WLC in clinical practice. One meta-analysis of prospective trials involving a total of 1,345 patients showed that, in comparison with WLC, HAL-FC significantly improved tumour detection and significantly reduced recurrence rates at 12 months, independently of patient's risk category and whether HAL was used at initial presentation or on recurrence. Furthermore, a retrospective analysis showed that HAL-FC can significantly improve recurrence-free survival and overall survival in patients undergoing TURB and subsequent radical cystectomy. The said benefits seem pronounced in high risk NMIBC. HAL-FC can also improve disease staging, resulting in more appropriate treatment selection, such as adjuvant chemo- or immunotherapy or early cystectomy. In a phase III study, 22% of patients with confirmed NMIBC had a change of treatment after HAL-FC compared with WLC ($p<0.001$).

Use of FC in the diagnosis of bladder cancer is recommended by the European Association of Urology (EAU), the International Consultation on Urological Diseases (ICUD) and the National Institute for Health and Care Excellence (NICE). The 2015 EAU guidelines and the second ICUD-EAU report recommend FC to guide initial TURB and biopsy and to aid diagnosis of carcinoma in situ (CIS). ICUD-EAU guidelines also recommend FC for patients with positive urine cytology but negative WLC. Numerous expert groups have addressed best-practice implementation of HAL-FC into clinical management of patients with NMIBC (Table 1).

In addition to improving patient outcomes, HAL-FC has been shown to realise both short- and long-term cost effectiveness, despite the initial cost of equipment. Results from a UK analysis suggest that, compared with WLC alone, adjunctive HAL-FC would be expected to result in 0.060 incremental quality-adjusted life years (QALYs) and a cost saving per patient of £391 (€516) due to fewer recurrences and recurrence-associated procedures. A German analysis reported cost savings with FC compared with WLC to be €168 per patient per year over a median follow up of 7.1 years. In an Italian analysis, use of HAL-FC improved the completeness of lesion resection and tumour staging, leading to a lower recurrence rate and fewer associated TURBs and hospitalisations, compared with WLC. The incremental cost saving was €435. For the incremental cost-effectiveness ratio, HAL-FC was dominant, compared with WLC, as a result of increased QALYs and lower costs over the short term. HAL-FC remained the dominant strategy in univariate sensitivity analyses, in which the key drivers of the model included the cost of HAL-FC, the cost of WLC-assisted TURB and relative risk of recurrence. In probabilistic sensitivity analyses, HAL-FC was expected to be dominant in 92% of iterations (Table 2).

In conclusion, incorporation of HAL-FC as an adjunct to WLC into the routine management of patients with NMIBC should be considered, given the significant benefits in detecting lesions, thus reducing recurrence rates and providing both short- and long-term cost savings.

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References can be obtained from the author or read the full story in internet.

Contact: mburger@caritasstjosef.de, maximilian.burger@ukr.de

Internet: www.healthcare-in-europe.com

Table 1. European expert consensus opinion and expert recommendations regarding HAL-FC

Setting	Recommendations			Consensus group statements			
	EAU[15]	ICUD-EAU[16]	NICE[17]	European[18]	Nordic[20]	UK[19]	US[26]
For guidance of initial TURB and biopsy	+	+	+	+	+	+	+
To aid CIS diagnosis	+*	+	+	+	?	+	+
To evaluate suspected recurrence	?	+†	+	+	+	+	+
During follow up in patients with high recurrence risk‡	?	?	+	+	+	(+)	+§
In patients who have received treatment with BCG	?	?	?	+	?	?	+
In patients with repeat resection within 6 weeks after TURB	?	?	?	+	?	?	?

*For follow-up in patients with CIS after TURB, random biopsies or biopsies with PDD after intravesical treatment (at 3 or 6 months) should also be considered
†Multifocal lesions
‡High-grade T1, multifocal or CIS lesions
§Intermediate risk of recurrence
+=recommended; (+)=tentatively recommended; ?=not reported
BCG=bacillus Calmette–Guérin; CIS=carcinoma in situ; EAU=European Association of Urology; HAL FC=hexaminolevulinate-guided fluorescence cystoscopy; ICUD=International Consultation on Urological Diseases; TURB=transurethral resection of the bladder

Table 2. Model lifetime results for the sample cost-effectiveness analysis

	HAL-FC	WLC	Incremental results	ICER (€/QALY)
Life years	11.003	10.970	0.033	
QALYs	8.06	7.99	0.070	
Recurrences and TURBs	1.30	1.54	−0.24	
Inpatient stays	4.56	5.02	−0.46	
Total cost	€28,086	€28,521	−€435	Dominant

HAL-FC=hexaminolevulinate-guided fluorescence cystoscopy; ICER=incremental cost-effectiveness ratio; QALY=quality-adjusted life year; WLC=white-light cystoscopy

Maximilian Burger is Chairman Professor of Urology and Chairman of the Department of Urology, University of Regensburg, since October 2013. He is also Fellow of the European Board of Urology, member of the bladder cancer guideline panel of the European Association of Urology (EAU), a member of the bladder cancer guideline panel of the German Association of Urology (DGU) and DGU-board member.

A procedure destined for extinction

pitals conduct t mortems

Angus Turnbull is a final year medical student at Imperial College London. His special interests are patient safety and autopsy with on-going study of the value of hospital autopsy in modern medicine and strategies to increase rates. Medical school highlights include a clinical quality improvement initiative in patient safety (looking at side room infection control) and a 1st class Honours BSc degree in Respiratory Sciences. He played an integral part in the implementation of an electronic early warning system to detect acutely deteriorating patients at York Teaching Hospital NHS Foundation Trust.

Turnbull: 'Over the past half-century, small single site studies have noted a marked decline in consented autopsy rates. However, there has been no study for over 20 years to determine the extent of the decline nationwide.'

Researchers believe there are a number of reasons for the decline:

- Physician belief that autopsy has no role in modern medicine due to improved diagnostics leading to accurate ante-mortem diagnosis
- Physician belief that families will rarely consent to the autopsy of a relative
- Physician belief that legal frameworks, such as the Human Tissue Act, prevent the consent for autopsy
- Religious objection to autopsy Adverse portrayal of autopsy in the media.

'All of this is perpetuated by a vicious circle - autopsy has been requested less by physicians, which mean fewer junior doctors know the benefit autopsy can bring,' he added. 'Few doctors of the future will request autopsy.'

A key reason for the decline is that confidence in diagnosis has risen with improved diagnostics, however he points out that the literature also shows that actual misdiagnosis rates remain high.

In addition, from his personal experience as a medical student, he said that nowadays 'many medical students will not attend a single autopsy throughout their training – yet a generation ago they were used in student teaching on a weekly basis.'

Whilst suggesting there are no alternatives as effective as the hospital post-mortem, there is a move – driven by religious communities – towards non-invasive 'radiological autopsies'.

'We believe these will be used more extensively in the future in replacing the classical Coronial Post-mortem,' he said. 'They will, however, have minimal benefit in replacing the hospital post mortem, because the majority of patients who die in hospital have already been extensively imaged radiologically and these autopsies do not provide the opportunity to use tissue samples for research purposes into the pathophysiology of diseases.' The practice of post mortem examination, or autopsy, dates back to mummification and human dissection in 3000 BC, but is thought to have entered medical practice in its current form in the 1800s.

Turnbull pointed out that the virtual extinction of consented autopsy should be of concern because it has the potential to bring multiple benefits to the medical community by aiding in clinical audit, quality assurance, public health, misdiagnosis, epidemiology and the teaching of trainee pathologists and medical students. It also has a value in the realms of medical research: in clinical trials it acts as a perfect end point, enabling research of medical procedures and surgical techniques; mortality statistics (huge progress has been made in neonatal and maternal mortality, in part due to findings from autopsy), and education of medical students. Evidence suggests the use of autopsies is also declining in Europe and the USA.

Turnbull concludes: 'Clinicians and patients should understand that autopsy, which once was of vital importance, has been reduced to a rarity in modern medicine. Unless the medical and lay community act now, then consented autopsy shall soon be extinct along with all the benefits it can bring.'

'Further research should be focused on quantifying the benefits of autopsy and examining the reasons for the decline in numbers. It should look at the impact that low autopsy figures have on patient safety, clinical audit and research, public health, and teaching.'

Refugees keep coming but Munich medics meet demands

The major healthcare challenge

Anaesthesiologist, intensive care physician and pain expert Bart Morlion MD is president-elect of the European Pain Federation EFIC. He studied at the University of Leuven, Belgium, and completed a specialist residency at the Ruhr University, Bochum, Germany. He returned to Leuven in 1998 to become professor in the Department of Cardiovascular Sciences and head of the multidisciplinary pain centre. From 2006 until 2012 Morlion presided over the Belgian Pain Society and is the principal investigator in 28 national and international multicentre clinical trials (Phases II, III and IV)

Report: Anja Behringer

The refugee wave rolls on with no ebb in sight. For many, Germany remains their travel destination. In August and September alone, tens of thousands refugees arrived in Munich, presenting the Bavarian capital with a major challenge: How could the city provide initial medical care for everyone? While the German Asylum Procedure Act governs the appropriate procedures, in this unprecedented situation it was necessary for everyone involved to act quickly, efficiently and, most importantly, less bureaucratically.

Due to its timely relevance, Dr Werner Schimana of the municipal health department was asked at short notice to speak at European Health Congress in Munich in early October. The paediatrician and adolescent medicine specialist reported how medical examinations are performed in tents at the central station in the course of registration, even before refugees are allocated to the initial processing facilities in the city and vicinity and then taken to other states. During this initial screening, teams containing two paramedics and a physician examine refugees; two teams can care for approximately 500-600 people within a 24-hour period.

Within three days an additional health examination is performed in the initial processing facilities. If need be, the refugees receive medical treatment, which is not always easy. Since both the federal and state authorities want to improve care of refugees, including healthcare, the draft Asylum Procedure (Acceleration) Act was adopted by the federal cabinet on 29 September 2015, with a supporting directive. As far as disease prevention is concerned, the states can also draw on the Robert Koch Institute and its 'concept for implementation of early vaccination of asylum-seekers'.

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Medical care with little bureaucracy

To provide non-bureaucratic assistance, the paediatrician Dr Mathias Wedeborn founded 'Refudocs', a Munich-based association that operates an acute treatment practice for refugees, financed outside the health insurance system. Since January, general practitioners, paediatricians, gynaecologists, and psychotherapists have been offering consultation five days a week in the initial processing facility at the Bayernkaserne for patients with acute illness, trauma or pregnancy.

They work on an hourly basis in addition to their regular work or, if retired, in the spare time. More than 70 physicians are on the association's roster, which functions as the practice owner. 'We are not only inexpensive. By virtue of our presence at the scene, we prevent many unnecessary emergency cases and hospitalisations,' Wedeborn explained. Moreover, examination results are entered in a database so that they can be assigned to the person even after the refugee's transfer.

The Oberbayern regional government, which assumed the start-up financing of this practice, pays Refudocs a contractually agreed, fixed hourly rate for medical service rendered. The association retains a portion to pay technical staff and practice overhead. The rest is paid to the physicians.

Immunisation: a first step toward prevention

At the beginning of October, the Robert Koch Institute (RKI) reported that there is currently only a very low risk of rare infectious diseases borne by asylum-seekers being imported into Germany. 'Analyses of reporting data on infection incidents in the past years show that more than 90% of those who were ill were infected in Germany. That means the asylum-seekers are more of a group at risk than a risk to others.'

The institute also provides a list of infectious diseases uncommon there, which can occur among asylum-seekers – inter alia malaria, typhoid or relapsing fever. At the same time the Institute stresses that an outbreak of these diseases among the general population is very unlikely. Rather, many refugees suffer more from scabies incurred during flight, or from being in cramped quarters.

According to Schimana, current examinations show that less than 1% of the refugees tested positive for HIV or hepatitis. Approximately 1% has TBC infections, whereby the number of suspected cases is higher, 'but that corresponds to the incidence among the German population and is manageable'. The next step in medical care to be performed is – nevertheless voluntary –vaccination, in accordance with the recommendations of the Standing Immunisation Commission (STIKO). Anyone who does not have a vaccination card is deemed unvaccinated.

According to the Asylum Procedure Act, the senior state health authority determines the scope of examinations for communicable diseases to be performed on foreigners who have to live in an initial processing facility or communal accommodation. The law prescribes that these people must submit a physician's certificate that there are no indications of infectious pulmonary TB. This certificate must be supported by a lung X-ray for all 15+year-olds (except those who are pregnant). That sums up the legal requirements.


Werner Schimana presented the initial assessment of refugee medical care at the European Health Congress

However, according to RKI 'The current high numbers of asylum-seekers presents the states with great challenges, also in organisation of health examinations, inter alia with regard to the required capacity for X-ray examinations. Hence there ought to be a technical reassessment of the procedure for thoracic X-ray exams of people 15 and older.'

Additionally, the Institute fears that a sharper increase in the illness is to be expected. It is estimated that one person suffering open tuberculosis – half of all new disease incidents – infects ten healthy people annually.

Another approach would be a triage using infection diagnostics (IGRA/ tuberculin skin tests) and a subsequent X-ray only if the test is positive. However, current test methods do not permit a distinction between active tuberculosis and latent TB infection (LTBI). Moreover, since the tests do not offer 100% sensitivity, a false negative finding is possible, even in a case of active TB. They are unsuitable for predicting the progression into a case of active TB.

German infection experts unite in a joint congress

Efficiency is vital to combat epidemics

Senior medical consultant and internist **Gerd Fätkenheuer**, President of the German Society of Infectious Diseases, has held an extraordinary professorship (in Germany a professor without chair) at Cologne University Hospital since 2004

Report: Anja Behringer

Efficient refers to faster diagnosis, more effective treatment and more information for medical staff as well as patients. The increasing resistance to antibiotics worldwide has led to the development of new infectious diseases and turned those that have been known for years into epidemics, such as Ebola or SARS.

In November, the German Society of Infectious Diseases (DGI) and the German Centre for Infection Research (DZIF) held, for the first time, a joint congress in Munich. 'The speedy development of vaccines against Ebola and other new infectious diseases is an important focus at the DZIF,' emphasised the organisation's chairman, Professor Martin Krönke.

DZIF researchers are not only involved in combating new viruses but also work against diseases such as AIDS, hepatitis, malaria, tuberculosis (TB) and gastro-intestinal diseases. A further focus is on beating hospital acquired infections. The increasing spread of antibiotic-resistant pathogens calls for new anti-infectives and an effective containment of resistant bacteria. DGI President Professor Gerd Fätkenheuer, who heads the Department for Infectious Diseases at the Clinic I for Internal Medicine, at Cologne University Hospital Cologne, is calling for the training of more specialists for complex infectious diseases, who could, in turn, also ensure appropriate training for other groups of doctors.

The WHO warns Europe

The World Health Organisation is warning of an HIV epidemic in Europe. This year there were 142,000 new infections, 6,000 more than in 2014. Eastern Europe was particularly affected, but because of the streams of refugees heading west the infections are unlikely to remain contained to that part of Europe.

TB has long been associated with poverty. At least eight million people a year develop the disease, with 5% of those being diagnosed with open TB – doubling the number of cases. Every year, 1.4 million people die as a result of this infection, meaning it remains one of the biggest health risks despite the enormous efforts involved in combating it. Co-infections with HIV and the spread of largely resistant and multi—drug-resistant (MDR) trains of bacteria and extensively drug-resistant (XDR) within the so-called Mycobacterium tuberculosis complex (Mtb-complex) further increase the problem. These MDR strains are increasingly spreading in Eastern Europe, Sub-Saharan Africa and Asia.

TB as a worldwide challenge

On a global level TB containment faces various challenges. There is currently no effective vaccine against pulmonary tuberculosis; effective medication against TB is scarce and the pharmaceutical industry has only few active ingredients under development. There is also a lack of biomarkers that can help to predict treatment success, or help to define the course of treatment more precisely. Less affluent countries also lack the resources for a fast diagnosis of TB cases. The diagnosis of the disease is particularly difficult amongst refugees because it takes several local examinations to confirm a diagnosis of open TB, but the individuals tend to be highly mobile upon arrival in Europe.

The laboratory at the Clinical Tuberculosis Centre (ClinTB) in the Medical Clinic Borstel, Schleswig-Holstein, is evaluating procedures for the individual characterisation of the endpoint of M/XDR tuberculosis treatment. The organisation and scheduling of seminars to help educate doctors and public health workers forms an important part of this work.

The development of a new 'online consultation service', through which specialists can discuss and agree on individual and efficient TB treatment, is also important, and so is the development and issuance of universal guidelines on the management of M/XDR-TB.

The infection can only be tackled with an interdisciplinary approach. The focal points of research are the examination of the genetic resistance of the pathogens to drugs and the identification of biomarkers that are to improve our ability to predict the treatment length needed for individual patients. However, there are many calls for the speedy development of vaccines; experts are not yet agreed as to exactly which of the pathogens should be tackled because they change in different outbreaks of the disease, and drugs will have different effects. One single vaccine per pathogen would therefore not be enough, and this is before there has even been a discussion about how to finance all of this developmental work.

Interdisciplinary use of antibiotic stewardship

Professor Fätkenheuer believes that the careful and intelligent use of antibiotics is essential to achieving relief, fast.

To this end, the DGI has founded the Antibiotic Stewardship (ABS) research initiative, which is utilised to train colleagues from clinical and diagnostic fields, as well as pharmacists, in responsible use of antibiotics. Strategies for this are accessible in the German-Austrian guidelines.

All of this could save lives.

Defining internationally common standards to assess bacterial resistance

Antimicrobial breakpoints

ESCMID past-president Professor Gunnar Kahlmeter MD , Sweden

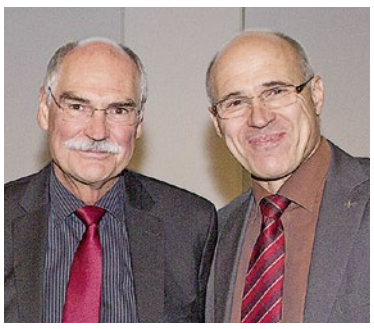
An antimicrobial breakpoint is an agreed concentration to identify at what point the growth of bacterium is inhibited – the minimum inhibitory concentration (MIC) – which essentially defines at what dose each bacteria is considered susceptible, or resistant, to antimicrobial therapy. Breakpoints of new agents are totally vital in standardising a global definition of resistance and the point at which increased dosages are needed.

Ninety percent of Europe's countries now follow the European Committee on Antimicrobial Susceptibility Testing (EUCAST) categorisation of bacterial susceptibility and resistance to new and existing antimicrobial agents – indeed, this uptake has snowballed with countries such as Australia, New Zealand and South Africa either already adhering to the EUCAST system or seriously contemplating adoption. This is considered a huge breakthrough in the committee's efforts to unify scientists and laboratories worldwide in their assessment of the bacterial resistance situation.

However, EUCAST is little known by the general public. Founded in 1997, it is fully known of as the European Committee on Antimicrobial Susceptibility Testing, a standing committee jointly organised and funded by the European Society of Clinical Microbiology and Infectious Disease (ESCMID), and the European Centre for Disease Prevention and Control (ECDC), as well as European national breakpoint committees. EUCAST aims to establish a common system to determine the defining and measuring of resistance. The new breakpoints currently worked on will enable increased conservation of new antimicrobial agents and ensure scientists are comparing like for like resistance.

Topical antibiotic therapy is an indispensable add-on

Locally applied antibiotics are a component of effective infection management in orthopaedics and trauma surgery. Successful concepts are based on patient-specific surgical and antimicrobial treatment. At the symposium "Infections and high-risk patients: solutions for joint replacements and traumatology" at this year's Congress on Orthopaedics and Trauma Surgery (DKOU) in Berlin last October, two experts discussed the best possible delivery of topical antibiotics.



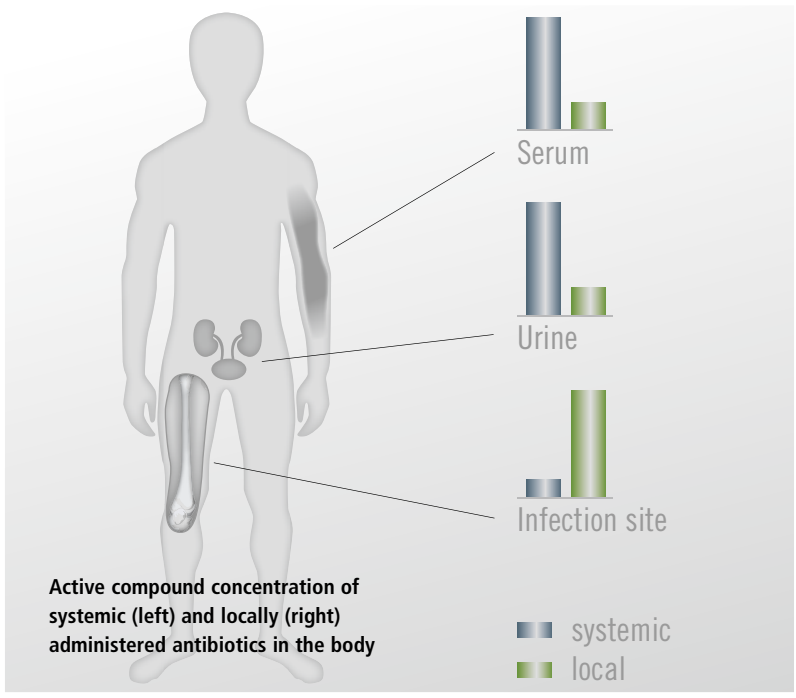
Professprs Volker Bühren (left) and Wolfram Mittelmeier at the symposium

Any orthopaedic or trauma surgery intervention can cause an infection – a risk which is particularly high when a foreign object remains in the patient's body, be it as a spacer or as the actual implant, as bacteria are prone to colonize the surface of objects. Thus, antibiotic therapy for infection prophylaxis is generally considered indispensible in orthopaedics and trauma surgery, above all in high-risk patients such as multi-morbid or polytrauma patients.

Risk management: a combination of topical and systemic antibiotics

With these patients, however, the efficacy of systemic antibiotics is limited, explained Professor Wolfram Mittelmeier, speaker at the symposium and Director of the Orthopaedic Clinic at the University Hospital Rostock, Germany, since scars and low haemoperfusion of bones prevent the antibiotic from sufficiently reaching the targeted area. In orthopaedics, he underlined, this is frequently a problem in multiple or subsequent surgeries with rather severe scarring.

In traumatology, low topical concentration of systemic antibiotics is usually due to peripheral hypotension and the severe bone and tissue damage caused by an accident, said Professor Bühren, further speaker and Medical Director of the Trauma Clinic Murnau, Germany. Thus the benefits of local delivery of antibiotics in orthopaedics and trauma surgery seem obvious: it ensure a sufficiently high concentration of the agent at the trauma site and reduces the side effects on the entire organism. Since to date there are few data supporting the long-term effect of topical antibiotics, the two experts agree, effective infection prophylaxis requires a two-pronged approach: topical and systemic antibiotic therapy. The crucial issue with this approach, according to Professor Mittelmeier, is the proper selection of suitable antibiotics. While all commercially available antibiotics can be used for systemic therapy, only certain ones are suitable for topical delivery due to various features of the carrier substances. Moreover, systemic antibiotics offer better and faster reaction to "hidden microbes" or to changes in the types of microbes present.



Active compound concentration of systemic (left) and locally (right) administered antibiotics in the body

Topical antibiotic delivery: cement is the gold standard

In addition to the conventional delivery of antibiotics, there are currently three methods to get topical antibiotics to the desired site: antibiotic-impregnated PMMA beads (polymethyl methacrylate), collagen sponges and cement. While both experts considered antibiotic-loaded cement the substance of choice, they did point out that even this option is far from ideal: on the one hand a certain degree of "abrasion" of the cement is desired in order for the antibiotic to be released into the body, on the other hand cement particles could settle in the surrounding joints and tissues increasing the infection risk. Despite these drawbacks, Mittelmeier and Bühren agree: at this point in time the antibiotic-loaded cement is the best option.

Differences between prophylaxis and therapy

Antibiotic-loaded cement is available industrially manufactured; but the antibiotic may also be added to the cement manually which ensures a very high degree of specific antibiotics release. With regard to prophylaxis in trauma surgery, Professor Bühren recommended the local concentration of the antibiotic to be above the minimal inhibitory concentration (MIC) in order to avoid the development of resistance. However, a concentration which is too high can have adverse effects on the healing process.

For orthopaedics Professor Mittelmeier recommends again a two-pronged approach: low dose for prophylaxis purposes, high dose to combat detected microbes. For permanent solutions - such as knee replacements - he strongly advised against manually adding antibiotics to the cement since any manual manipulation of the cement carries the risk of reducing the mechanical performance of the cement – a potential problem since the surgeon is liable in case the surgery fails.

In addition to the dosage the retention time in the body plays a major role. Both experts recommend not leaving cement-loaded spacers in the body for too long. Ideally they should be removed after six to eight weeks in order to avoid bacterial colonisation and to ensure that not too many particles are released. Nevertheless, the decision to remove the spacer is closely linked to the results of microbe testing. Case by case decisions are required.

By way of closing, both experts underlined that even the best antibiotics combination does not necessarily avoid and treat an infection – the crucial element is noq. and will be, the quality of the surgical intervention, including meticulous debridement.

Reducing arthroplasty revisions: cutting costs and improving patient satisfaction

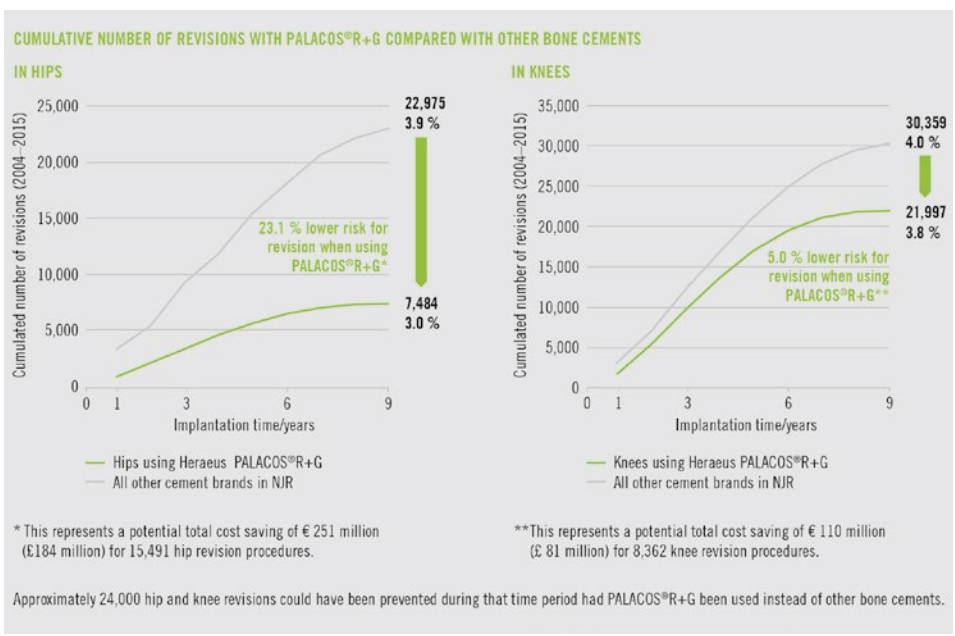
Use of antibiotic-loaded bone cement significantly lowers revision rates in hip and knee arthroplasty

Infection is a burdensome complication of all types of surgery and especially following arthroplasty. Implant removal and revision arthroplasty have a considerable impact on the patient and are associated with substantially greater hospital and physician resource utilisation, resulting in significantly higher costs compared to primary total joint arthroplasty. The use of antibiotic-loaded bone cements is a widely-practised method of reducing orthopaedic infections. The major appeal of incorporating antibiotics in bone cements is the higher local concentrations of antibiotic achievable when it is delivered in this way, compared with intravenous administration. PALACOS® R+G (Heraeus Medical), which includes gentamicin, has been in use for over 40 years.

At the Annual Meeting of the British Orthopaedic Association (Liverpool, September 2015), Heraeus Medical sponsored a satellite symposium to discuss "Infection in the high risk arthroplasty patient". "We need to reduce arthroplasty revisions as a quality measure" commented Mr Mike Reed, Consultant Trauma and Orthopaedic Surgeon at Northumbria NHS Healthcare Foundation Trust, UK, who spoke at the symposium. Mr Reed presented recent data from the National Joint Registry (NJR) of England, Wales and Northern Ireland (the largest arthroplasty registry worldwide) supporting the efficacy of antibiotic-loaded bone cements in the prevention of revision surgery. The data, spanning 2004–2015, comprised 717,339 cemented total knee and 421,604 cemented total hip arthroplasty procedures. Of those, 47% and 59% of primary hip and knee arthroplasties respectively were performed using PALACOS® R+G. Results showed a statistically significant reduction in the number of both hip and knee arthroplasty revisions when using antibiotic-loaded bone cement, specifically PALACOS® R+G, as compared to other bone cements.

Mr Reed set up a randomized trial of 848 patients undergoing hip hemi-arthroplasties; a good proxy for high risk arthroplasty patients due to the high infection rate observed in hip hemi-arthroplasty patients. Patients receiving high dose dual antibiotic cement (COPAL® G+C, containing gentamicin and clindamycin; Heraeus Medical) had significantly reduced surgical site infection rate compared to those receiving standard antibiotic-loaded cement. Mr Reed discussed how in his institution all lower limb joint replacements are carried out using antibiotic-loaded cement, using high dose dual antibiotic cement for patients with a hip fracture requiring joint replacement. Commenting on whether cost may be an issue, Mr Reed noted "We've done a significant cost analysis and it shows that even though high dose dual antibiotic cement is more expensive, the cost to the hospital and the NHS is reduced, because of the infections prevented".

Mike Reed, Consultant Trauma and Orthopaedic Surgeon at Northumbria NHS Healthcare Foundation Trust



A pathologist's work is undergoing radical transformation

I saw the future of pathology – and it's digital

Healthcare is going digital. No doubt about it, Prof. Hufnagl predicts. Information and communication technologies have gone beyond moving data from one place to the other; they are triggering stellar improvements in healthcare: diagnoses are becoming ever more precise, therapies ever more personalised. The extent to which the individual clinical disciplines have progressed in their technological development varies greatly. In pathology, for example, change has only just set in. However, it is already obvious, that digitisation will change the discipline forever. *Karoline Laarmann reports*

Scepticism towards digital systems is still widespread and fundamental questions regarding the sense and purpose of the new technology in the pathology department continue to be raised. These concerns are primarily caused by the significant necessary financial investments in hardware and software.

Basic equipment encompasses slide scanners, data storage devices and an image management system. There are many opinions as to whether and when the purchase of these digital pathology devices makes economic sense. However, there are – throughout Europe – very encouraging examples that demonstrate the successful step-by-step transformation from microscope-based histopathological diagnostics to digital diagnostics.

'Unfortunately, these positive examples are not sufficiently publicised in the pathology community', says Professor Peter Hufnagl, Head of Digital Pathology at the Institute of Pathology at Charité, Berlin, and President of the13th European Congress on Digital Pathology in Berlin in 2016. 'The two types of workflow, digital and analogue, can co-exist very well and, for some institutions, such a two-pronged approach might be the best solution in the long run. That means you don't have to wait until you can afford fully-fledged digitisation. Start small!'

Workflows in the pathology lab will benefit with only one third of the diagnostic task being digitised. Communication with clinicians will become faster, simpler and more effective. For large institutes involved in research and teaching complete digitisation makes sense, Professor Hufnagl underlines: 'The bio-banks being established in the academic environment particularly profit from a digital slide archive, since it allows larger sample groups to be selected and to check whether certain slides are suitable for a research project.'

While many pathology labs are still hesitant to jump on the digital bandwagon although the industry has recognised the market potential long ago and is actively driving its rapid growth through technological innovation. The fact that the use of a virtual microscope saves a lot of money on expensive samples is only one of the arguments manufacturers use to lure new customers. More importantly, however, digital pathology optimises quality assurance and thus contributes to a lab's competitiveness. Digitisation provides a better overview of comparable cases; it allows the application of quantitative methods to check diagnoses and accelerates obtaining second opinions.

Hufnagl is convinced that it is only a matter of time before digital pathology will prevail. In radiology, he points out, there were very similar concerns regarding on-screen readings – today this is standard operating procedure. The fact that, due to image volumes in pathology – 150.000 x 300.000 = 45000Mpixels – digitisation is taking root 20 years later than in radiology, is an advantage. We can learn from radiologists' experiences and from many of their solutions, because they can be translated into the questions that need answering in pathology.' Having said that, there are indeed also fundamental differences between the two image-based disciplines. The different CT slices, for example, are automatically adjusted – a step that is not so easy with histopathological samples that consist of three-dimensional tissue, such as a tumour. 'The registration of slides with different stains from the identical block is sometimes difficult. Differences between slides, such as pressure points, tiny fissures etcetera are originated by mechanical alterations in the lab or changing the lab during processing. Software programmers have not yet found a solution to deal with all different artefacts in a sufficient manner.'

In addition to diagnostics with the virtual microscope, digital pathology is being pushed ahead by other technological innovations, such as molecular pathology, particularly Next Generation Sequencing (NGS). This procedure can detect gene mutations much faster and simpler than before. This allows inter alia precise characterisation of tumours, which in turn translates into customised cancer therapies. Today NGS is considered the path-breaking technology towards personalised healthcare, because it is expected to have a crucial impact on diagnosis and prognoses of cancer and other diseases.

'Thus digitisation makes pathology much more visible in the landscape of clinical disciplines', Peter Hufnagl confirms, adding: 'This development is being supported on the organisational level, for example by the establishment of tumour boards that include pathologists and it will be accelerated by the new technologies.'

Peter Hufnagl, Head of Digital Pathology, Charité Berlin

Consequently not only the work environment and the 'job description' of a pathologist are undergoing radical transformation; the image of the pathologist is also changing. For years, pathology has been struggling with recruiting problems. Digitisation is giving the field a fresh, modern look and more junior physicians are becoming interested in this field. ■

Experts are discussing data volumes not yet seen in medicine

Automation in pathology

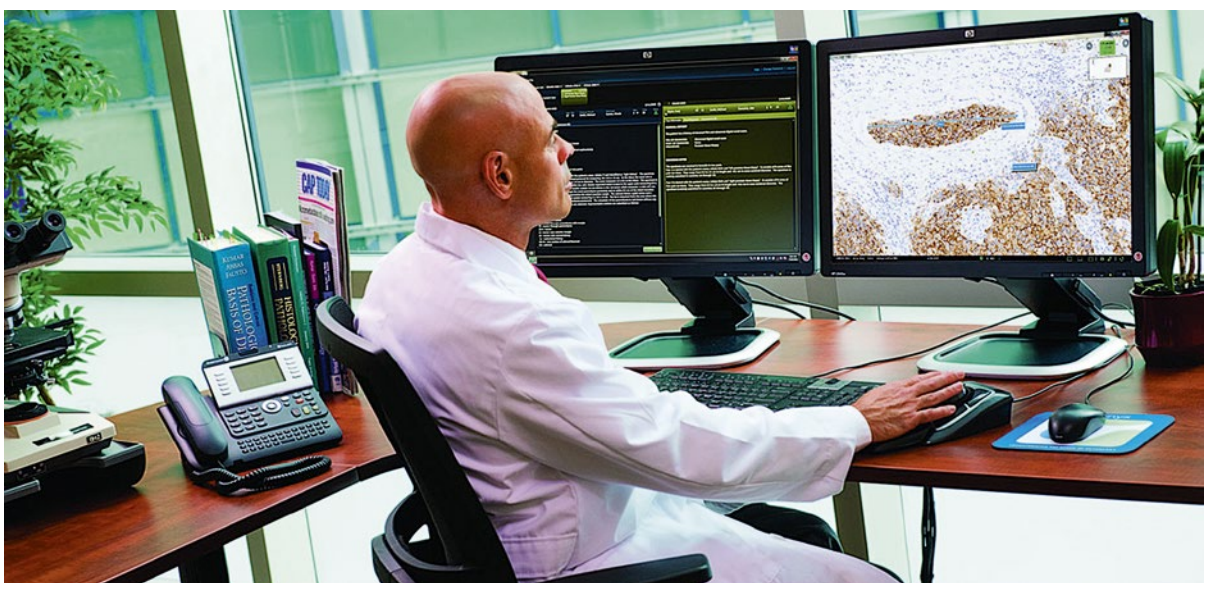
Surveying medical developments over the last two or three decades confirms the enormity of progress made during this period. Going into details would go far beyond the scope of this article, writes Walter Depner. 'However, one topic should be highlighted – pathology – because it has bucked the general trend in a certain way

For years, even decades, proven and successful methods and procedures have been used in pathology, involving intensive manual work, with a relatively little automation. This difference between other medical disciplines is now seeing rapid change. Automation in pathology is now frequently discussed in many publications, congresses and workshops etc. – as well as in our journal European Hospital, with topics from this field more frequently featured. In one such example (issue 4/2014, page 7) Professor Alessandro Lugli, at the Institute of Pathology in Bern, Switzerland, details the introduction of the Lean Management System in pathology.

The system was adapted from the automotive industry, in which it is utilised to improve quality as well as save costs and thus increase efficiency. After three years of using the Lean system in Bern, Lugli could confirm those benefits for the Institute of Pathology as well.

In this issue you can also read the opinions of Dr Bela Molnar (Budapest), one of Europe's pioneers in pathology automation.

We are now entering a further stage in the development of modern pathology, or respectively of automation in pathology – digital pathology. What does that term mean? Simply, it stands for the increased use of IT systems and, in other words, the transformation of histopathological results revealed with an analogue microscope to diagnostics, or the computer respectively.



This requires high-resolution scanning of samples of tissue sections so that they can be digitised in the computer. In theory, a tissue sample under the microscope offers several thousand fields of vision, but only one or two percent are actually relevant. With a digitised object however, after further assessments and documentation, we can immediately return to the important parts. This procedure also makes exchange with other national and international experts far easier. With the help of teleconferencing, or telepathology, experts can exchange knowledge and experience or seek second opinions on digitised histological samples in real-time, which obviously also enhances patient care. However, it still remains very uncertain as to what extent and how quickly digital pathology will become established in clinical routine. The systems are currently mainly used in academic and scientific settings, where digital sample scanners and the respective archiving systems are predominantly used for teaching purposes. On the other hand, demand for diagnosticians is growing and pathologists also need to deal with an increasing number of non-medical tasks and issues.

Says Dr Gian Kayser, Senior Consultant at the Institute for Pathology at the University Hospital Freiburg: 'The technology will certainly become more affordable and of higher quality in the foreseeable future. Within the next five to ten years an increasingly growing number of pathologists will be working completely digitally.'

Radiology is a particularly appropriate example. We should bear in mind that digitisation in this field literally began more than 40 years (!) ago with the introduction of CT scanners, at a time when no one really believed in a real breakthrough and introduction of this technology on a broad scale. Transferred to the current situation in pathology we can just about imagine the massive changes this medical area will face in the near future. However, unlike in radiology, one of the main problems here is the enormous amount of data.

Experts are in fact talking about the kinds of data volumes not yet seen in medicine. Of course, even in the world of radiology it was initially hardly conceivable how the PACS (Picture Archiving and Communication Systems) would cope with information overload. Nowadays, a radiology practice is basically inconceivable without 'digital diagnostics'. And maybe the same will apply to pathology in 20 or 30 years' time? As in radiology, the introduction of such a complex system will generate enormous costs and administration and data archiving (with data retention requirements of many years) will play an important part. Let's hope that Kayser's prognosis is correct. ■

Digital pathology algorithms will be in the lab in the next five years

Scaling the barriers to precise diagnoses

Dr David Snead is Consultant Cellular Pathologist with University Hospitals Coventry & Warwick NHS Trust and Director of the Digital Pathology Centre of Excellence. His main research interests are digital pathology as applied to routine diagnostic histopathology and lung cancer research.

Report: Mark Nicholls

Whilst digital pathology has the potential to deliver more precise diagnostics, there remain a number of barriers to its widespread implementation.

Cost, as with any new technology, remains an issue particularly against the backdrop of financial constraints experienced within, for example, the UK's National Health Service (NHS).

Doubts remain over whether digital methods are as good as traditional ones and there are also IT challenges in sharing data across national and international boundaries.

One of the UK's leading digital pathology experts, Dr David Snead, focused on these challenges when he addressed the international Global Engage 2nd Digital Pathology Congress in London (3-7 December 2015). In his presentation, Overcoming Barriers in Adoption of Digital Pathology, the consultant outlined the challenges, opportunities and potential that digital pathology offers for a new era of diagnostics and healthcare.

As Consultant Cellular Pathologist with University Hospitals Coventry & Warwick (UHCW) NHS Trust, Snead believes research, conducted by his team and others, is demonstrating that digital pathology is as good as traditional methods. 'We've answered these doubts with our validation study where we demonstrated that we can do 90% of the job on a digital platform that you can with a microscope.'

Cost remains an issue, but indications are that, as more manufacturers enter the market over the next 4-5 years, competition will drive down price and see greater implementation of digital pathology systems.

An issue, particularly facing the NHS, is that of sharing data with regulations and a lack of clarity, agreements and protocols on data sharing rules, security and confidentiality, he suggested.

What remains clear to Snead, who also heads the UHCW Centre of Excellence for Digital Pathology, is the potential of the technique. 'It's clear to me as a pathologist that digital pathology offers an increase in quality which we do not have yet,' he said. 'But, within a couple of years, authorities will accept there is a need to acquire and pay for this increase in quality that it offers.'

The Coventry centre, as an early adopter of digital pathology, is championing the case within the UK and with support and funding from the trust management is 'geared to providing pathologists with the tools they need to make digital pathology work for them'.

Snead: 'These will be tools which grade cancer more accurately and grade intensity staining in biomarkers in an entirely quantitative, reproducible and robust way, which we cannot do at present. What is done by the pathologist's eye and judgement at the moment is not good enough for today's treatment. Breast cancers are still being reported with varying degrees of their grade and patients require much more robust analysis, particularly in cancer treatment of the tumours they have.

'That's what excites us about digital pathology, about really improving pathology because we can now measure things we could not measure before.'

The Centre of Excellence has seven PhD students, two post docs and a computer scientist, working on digital pathology algorithms with the trust's partner, the University of Warwick. 'In the next five years we will see those algorithms in the lab, Snead predicts, 'delivering better assessments of pathology slides than we get at the moment and, I think, when we get to that point will be when digital pathology is really going to take off.' He recognises that, in Europe, health systems are not necessarily facing similar issues as the NHS, in part due to the different configuration of healthcare in comparison with that of the UK. Sweden, Spain and Holland are making strong progress as individual hospitals, institutions and heath organisations introduce their own initiatives.

However, Snead is confident that digital pathology will overcome barriers against its implementation. 'Everybody will be using this technology in 10 years because they will have to,' he said. 'There will not be any other way of doing it.'

SPECIAL: DIGITAL PATHOLOGY

Higher costs and increased expenditure on time and resources are limiting factors

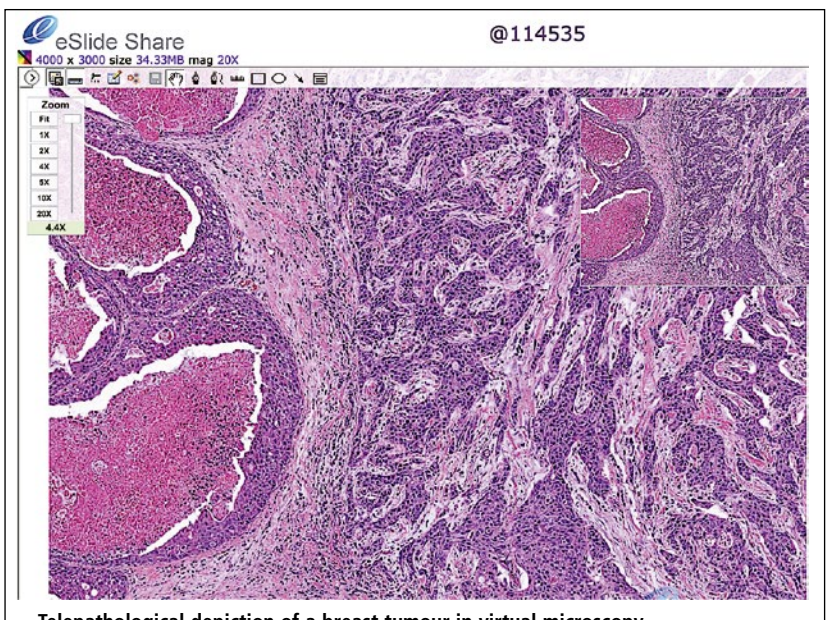
Telemedicine in pathology

Professor Hans-Peter Sinn MD, from the Division of Gynaecopathology, Heidelberg University Hospital

Increasing requirements for specialisation and diagnostic quality in pathology, on the one hand, and the importance of pathology findings for treatment planning, on the other, call for new solutions in pathomorphological diagnostics. One important starting point is the fast-paced opportunity for digitisation along with communication systems that can facilitate the storage and transfer of very large data volumes.

These open up new opportunities in pathology summarised by the term digital pathology. 'The term stands for procedures which facilitate improvements in quality and improved exchange with colleagues in the same field who may have a different or special expertise in certain areas. It also serves the improvement of communication with hospitals, both internally and across larger distances,' explains Professor Hans-Peter Sinn MD, who works at the Institute of Pathology at Heidelberg University Hospital.

Telemedicine in pathology used to be termed 'telepathology'. But this only means that a diagnosis is carried out over a certain distance for conventional preparations. It has a historical background, as there were efforts in the 1990s to transmit diagnostic images via bundled ISDN lines or similar, i.e. using outdated means that have long been abandoned due to the unsatisfactory technology and limited validity. Pathology and, in particular, tumour pathology, is increasingly integrating non-morphological procedures such as NGS (next generation sequencing) on which classifications are dependent. Histological preparations are now primarily digitised and made available by the server via virtual microscopy. 'The term 'digital pathology' not only comprises the transmission of images but also their metadata and additional information concerning the case, which the pathologist can use to gain a more complex understanding than with a microscopic image alone,' Professor Sinn explains.



Telepathological depiction of a breast tumour in virtual microscopy

Digitisation in pathology facilitates improved standardisation, transparency and digital archiving of microscopy. However, there is also another important factor. 'Telemedicine in pathology allows the networking of pathologists with one another in an uncomplicated way, particularly with regards to specialist areas of expertise. There are networks for haematopathology and gynaecopathology where content about histological preparations, research concepts or molecular procedures can be exchanged,' Sinn reports.

Telemedicine not only concerns patients and individual cases but also includes continued education, quality circles, lecture series, tumour registers and reference centres.

Is everything positive, then? By no means! 'The process of digitisation is unstoppable, but in the case of routine pathology has only just begun and poses particular challenges to this field.

This concerns, for instance, the lack of standardisation of platforms, image formats and interfaces of virtual microscopy with pathology- and hospital information systems.
Currently, there is also a lack of non-proprietary solutions for the networking of subsystems for molecular pathology as well as immunohistochemistry.'

Furthermore, financial aspects also play an important role. It would be misleading to assume that digitalisation and electronic provision of histological preparations and results definitely lowers costs per se by, for example, assuring that duplicate examinations are avoided. 'This is not actually the case with digital pathology,' says the expert, and substantiates this.

'Digitising histological preparations, or other pathological findings and making them available electronically for transmission if necessary, involves higher costs. We depend on the conventional histological, immunohistological and molecular methods and then we have to digitise them in a secondary procedure.

Therefore, digitisation is a secondary, expensive step. These days it is still easier and cheaper to put samples into envelopes and send them off. The costs of digital pathology are in the high six-figure range and therefore significantly higher than exchanging preparations in the conventional way.' The amounts of data that need processing are a further problem: 'Due to the microscopic resolution needed, the image data takes up a lot more storage space than data stored in radiology, for instance. A single histological preparation, once digitised, converts into around one gigabyte of data. If we want to digitise our entire microscopic diagnostics we would generate several hundred terabytes of data a year and, over a period of several years for routine image documentation in microscopy for just one institute, would end up in the petabyte range. This is another reason why digitisation in pathology is still a lot less common and standardised than in other areas of medicine,' the expert points out.

Sinn is essentially in favour of further digitisation, which, as said, he believes to be unstoppable. However, he warns against being naïve about this: 'The introduction of telemedicine on a broader scale primarily improves the quality of care, and only secondarily the efficiency.

'In the future this is going to result in the opportunity to work more objectively and in a more networked manner through the increased digitisation of medical results. Therefore, the patient has the potential advantage of improved care, but higher costs and significantly increased expenditure regarding time and resources are limiting factors, particularly for pathology.'

Digital pathology augments biomarker research

Taking biomarker research to a new level

Harnessing the potential of digital pathology is taking research into new and more efficient biomarkers to a new level, *Mark Nicholls* reports

By combining strategic planning with the latest digital pathology technology, high quality tissue microarrays for biomarker research are being produced.

This December, at the Digital Pathology Congress in London, the application of digital pathology in this area was highlighted by Professor Inti Zlobec from the Translational Research Unit at the Institute of Pathology, University of Bern, in Switzerland,

Her presentation on the 'Application of digital pathology to the construction of high-quality tissue microarrays for biomarker research: The next-generation tissue microarray (ngTMA) approach' demonstrate how digital pathology can be applied to construction of tissue microarrays. 'The inclusion of digital pathology into our tissue microarray workflow means we can have very high quality tissue microarrays that also allow us to address research questions we could have never answered before,' she told European Hospital, ahead of the international meeting.

Zlobec explained that by using digital pathology constructing tissue microarray becomes more efficient and precise. In an example where a biomarker needs to be examined on 500 tissue blocks, small cores can be punched out from each tissue and repeatedly transferred into an empty paraffin block to produce a tissue microarray. 'Tissue microarrays are a way of putting together an archive of all of these different patients material into one single block,' she added.

The process effectively creates a tissue microarray that contains dozens, or even hundreds, of different tissue cores, ranging in size from 0.6 to 2.0mm in diameter that contains selected regions for transfer into the TMA. 'This would have been impossible without digital pathology,' she confirmed. 'Before, we had to approximate from where we would be taking out those tissue cores, but now, because we have digital pathology, we know exactly which region we want transferred out from that block.'

This is a 'more specific, targeted and efficient' approach. However, Professor Zlobec believes at Bern they take the approach one step further by defining their ngTMA approach by three pillars: planning and design; application to digital pathology; and automated tissue micro-arraying.

'The planning phase makes or breaks the TMA quality, so regardless of how big the project size is – 10 patients or 1,000 – the planning is a critical point,' she explained.

Examples of key questions to keep in mind are: does the research question require a targeted ngTMA approach or can it be achieved without digital pathology; what histological regions need to be captured to answer the research question; how many patients does the project need to achieve the required statistical power; and how many cores should you use to account for the possible heterogeneity in the tissue??

'These are questions we never really asked before, when we did not have this new ngTMA approach,' Zlobec added. 'Once we have the plan and a corresponding slide we scan it, view it, annotate it, and finally align it with the actual tissue block from which it came. The annotated regions are cored out and transferred so, in the end, we have this amazing and precise ngTMA block, which can be cut and prepared for biomarker analysis.'

The Bern team also creates ngTMAs of animal models of human disease for comparison. There are significant benefits for clinicians, researchers and patients.

'On the one hand, we have an ngTMA approach that allows for high throughput biomarker screening and, on the other, allows us to go in-depth to answer targeted research questions that can only be addressed because we have this digital pathology aspect.

'We can apply our approach to a large number of patients in a way that is very cost-effective and resource sparing in terms of tissues, consumables and time in the lab. 'Because we can make these digital annotations on scanned slides we can construct ngTMA in a very precise manner and for the first time we can study important interfaces inside the tissue.'

Additionally, in cancer biomarker research, for example, intra-tumoural heterogeneity can be explored with ngTMA by annotating different regions within the tumour.

Also, because the slides are digital, the pathologists can go back to the annotation and see what exactly was cored out from that block, ensuring high levels of quality control.

Such use of ngTMA helps to create standards for biomarker research and, because tissues that are included in a block undergo the same experimental conditions, this means that variability from batch processing can be considerably reduced.

'All of these aspects combined mean we achieve high quality biomarker research and validation that can hopefully be more effectively translated back into patient management,' she said.

The next step – as well as challenge – is the quantification of the biomarkers using image analysis software to objectively measure the biomarkers, which in effect 'opens a whole field of digital pathology research'.

Inti Zlobec PhD is professor and head of the Translational Research Unit at the Institute of Pathology, University of Bern, where she is involved in interdisciplinary translational research that aims to improve the clinical management of patients with colorectal cancer. Her research also focuses on histomorphological biomarkers as prognostic and predictive features of tumour response to therapies.

Digital microscopy will upgrade u

Digital pathology: a new diagnostic technology

Histopathologists play key roles in diagnosing disease entities and determining biomarkers related to the prognosis and response to specific therapy of malignant tumours

Histopathology is still firmly based on cell and tissue morphology supplemented with in situ molecular information and these together can be studied using an optical microscope.

Digital microscopy creates a digital representation of the whole microscopic slides at decent quality, which can be dynamically viewed, navigated and magnified via a mouse and computer monitor, and shared though computer networks without spatial and temporal limitations.

Digital slides can be integrated into the hospital information system (HIS) and accessed through intra- or internet for teaching, primary diagnosis, teleconsultation and quality assurance.

Discrete pixels of calibrated qualities allow automated image analysis and signal quantification for drawing unbiased conclusions in diagnostic and research applications. Therefore, utilisation of the full power of computer technology to access multiple functions and the internet grants digital microscopy great potential to upgrade the efficiency of pathology workflow and pathologists. By resolving critical issues, including standardisation of data formats, secure and fast internet communication and medico-legal aspects, digital microscopy is expected to play a revolutionary role in future histopathology.

Digital slides created by slide scanners

Digital microscopy creates large digital files representing all crucial details of stained tissue sections with decent resolution and high colour fidelity achieved using automated focusing and white balance. Digital slides are made up of giant arrays of rectangular pixels organised along x-y coordinates, each of which is characterised by size, colour and intensity values.

Produced either by area or line scanning, digital slides are built up as pyramids of microscopic image series where low power views are generated by compressing the original sharp and optimally lit images (Fig. 1A). Scanning through several focal levels within the usual 3-8µm sample thickness offers access to the z dimension used for emulating fine focusing of the optical microscope. Fig. 1 A) The \image series by compression allows viewing of the digital slide at arbitrary magnifications (e.g. x15 and x10). Scanning at different focal levels within the sample thickness (~3-8µm) offers access to fine details in the z-dimension.

Using x10 lens offers high field of view (FOV) size and focal depth, while requiring small storage space. A x20 objective allows double the optical resolution than that of x10, but at the expense of revealing smaller FOV and focal depth, while increasing the storage need. x40 objective does not offer significant improvement in optical resolution compared to x20 (NA=0.9 vs.0.8) despite needing large storage space and long scanning time.

Unique features of digital slides

Seeing slides on a monitor, with easy access to a computer's multifunctionality, is far more ergonomic than peering though an ocular lens of an optical microscope. Even pathologists with high affection for conventional microscopy respect digital microscopy benefits if they practise enough. The computer-generated image pyramid format of digital slides allows in-focus navigation through continuously changing magnifications, without changing objectives, or realigning the focus or lighting conditions. Digital magnifications beyond that used for scanning still reveal fine microscopic details hidden in the original magnification.

Slides can be tilted arbitrary for proper orientation and preview images of the whole slide are available simultaneously on the monitor where navigation history of high power analysis can also be traced (Fig. 3). Fig. 3 A) Digital slide viewer interfaces utilise the whole computer monitor where preview images and navigation history (left side) of high power analysis can also be traced. Calibrated pixels allow straight measurements of object distance, perimeter or area highlighted by permanent annotations. B) The monitor can be shared for several digital slides for comparative studies, as shown by the same area of serial slides stained for H&E, the proliferation marker Ki67 (brown; middle) and the gap junction connexin-43 (red immunofluorescence) combined with the Ki67 protein (green; right), respectively in oral epithelial hyperplasia.

Permanent annotations and text put on digital slides, straight measurements of object distance, perimeter or area and prompt still-image

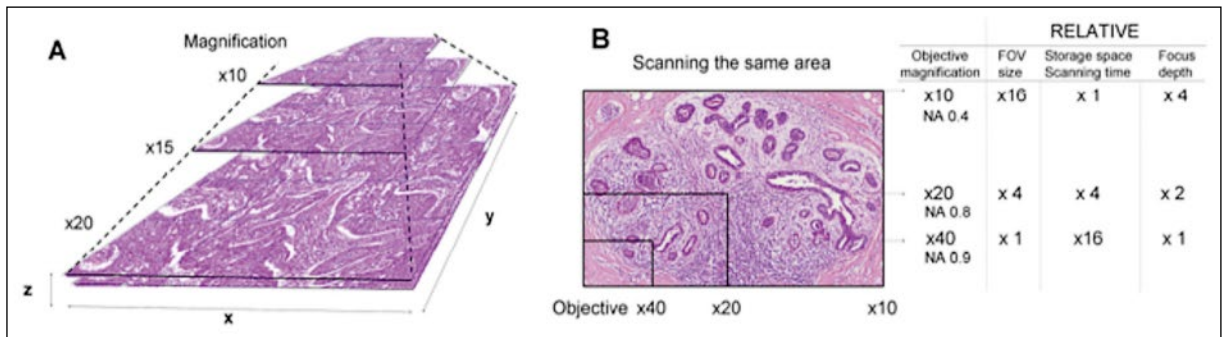
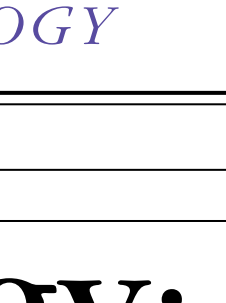


Fig. 1 A) The image pyramid generated from optimised x20 magnification image series by compression allows viewing of the digital slide at arbitrary magnifications (e.g. x15 and x10). See details wihin the article.



Bela Molnar MD DSc is CEO of 3DHISTECH Ltd, which has developed high-performance hardware and software products for digital pathology since 1996. A medical graduate from Semmeweis University, Budapest, and the Hungarian Academy of Sciences, he gained qualifications as an internist and gastroenterologist, followed by a post doctoral 2-year fellowship with Boehringer Ingelheim GmbH. Scientific/industrial cooperation arose with Roche Diagnostics, Epigenomics Inc (Seattle/Berlin), and Carl Zeiss MicroImaging. Today, Molnar's main research areas include biomarkers of colorectal cancer development, molecular biology applications, virtual microscopy, and quantitative image analysis, and his publications, memberships of scientific bodies and professional awards are numerous.

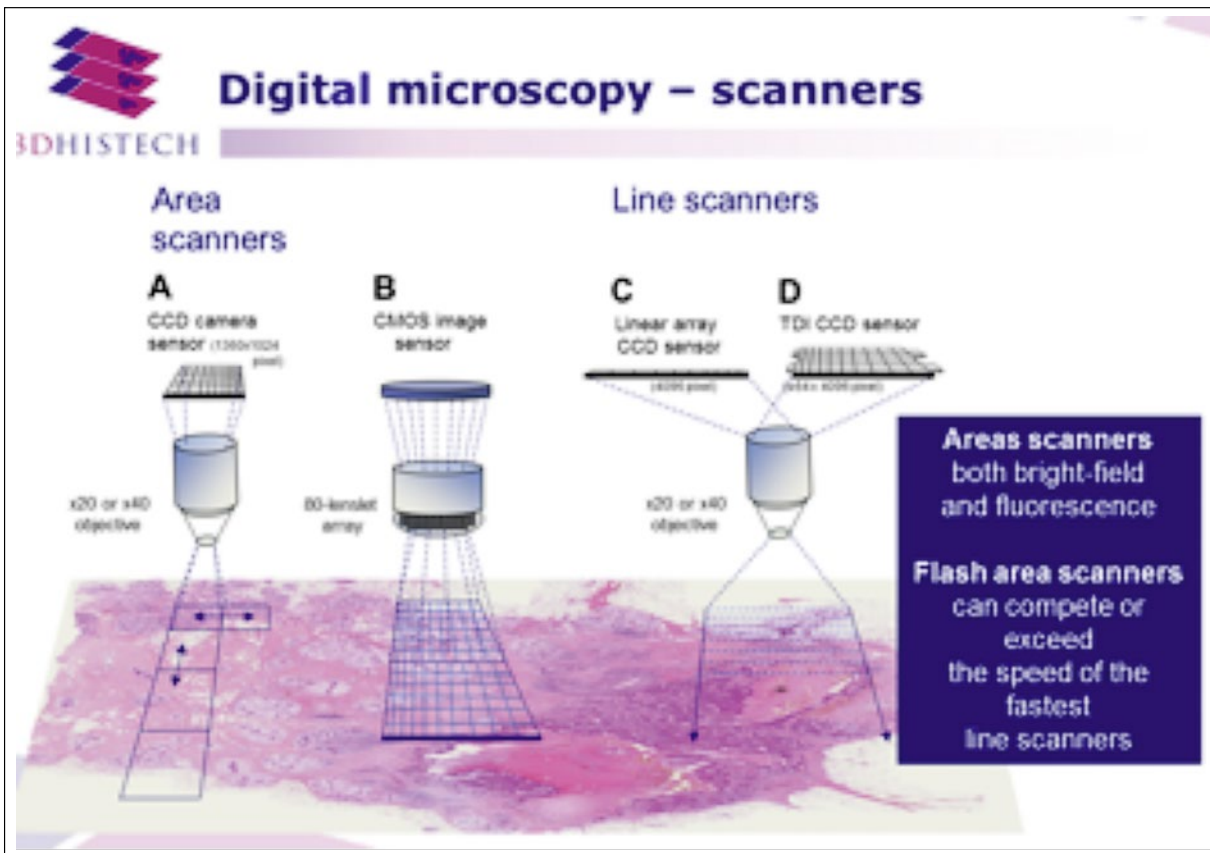


Fig. 2 Schematic representation of area scanning (A, B) and line scanning (C, D) techniques used by available slide scanners. A) Classical area scanners collect large series of images at x-y dimensions through a microscope objective with a CCD camera, either in bright-field or fluorescence mode. B) The area scanner combining an 80-element lenslet array with complementary metal oxide semiconductor (CMOS) sensor can cover large section areas at once. C) Typical line scanners can collect image strips from the continuously moving slides through an objective using a linear array light sensor, which is, however, not sensitive enough for fluorescence signals. D) Combination of 64 or more of linear array sensors permits TDI (time delay and integration) scanning, where consecutive sensors cumulate the signals making TDI appropriate also for fluorescence scanning

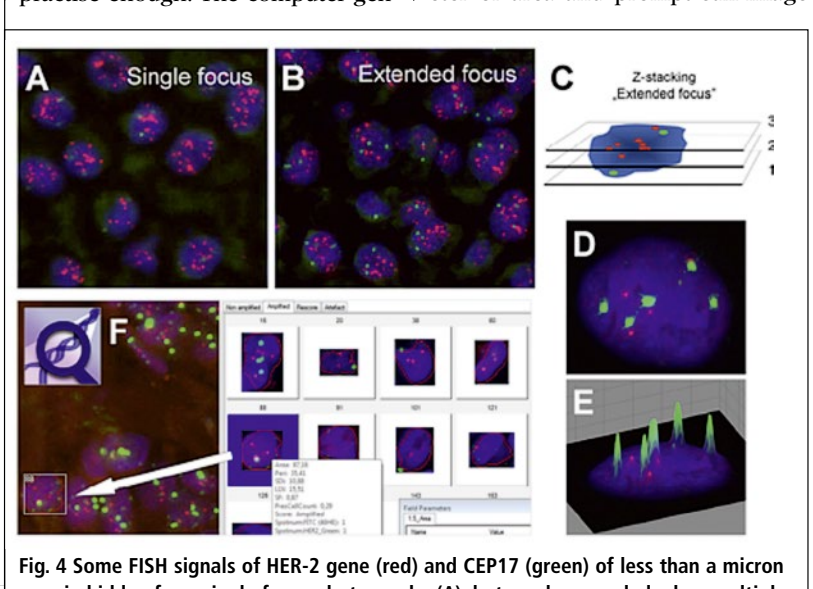


Fig. 4 Some FISH signals of HER-2 gene (red) and CEP17 (green) of less than a micron remain hidden from single focus photography (A), but can be revealed when multiple focus layers are scanned and then projected (B; extended focus). Please note that several green signals that are missing from A are clearly seen on B. C) Accumulation of all red and green signals gained from merging consecutive optical layers allows reliable analysis. D) FISH (fluorescence in situ hybridisation) signals revealed in a cell can be intensity-amplified in 3-D (E) for better assessment. F) Cell nuclei can be automatically sorted into groups in a gallery according to their FISH pattern and re-localised into their tissue environment.

workflow and specialists' efficiency

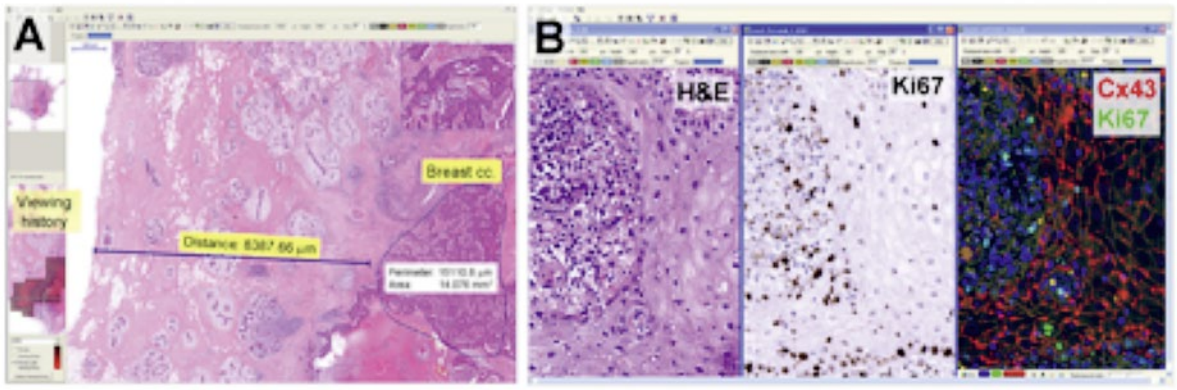


Fig. 3 A) Digital slide viewer interfaces utilise the whole computer monitor where preview images and navigation history (left side) of high power analysis can also be traced. See details within the article.

Fig.5 Digital pathology integrated in the routine workflow processes. Imaging of the grossing, different slide stainings are combined into one digital case, which is then later evaluated on a digital pathology workplace. The quantitative analysis is an integrated part of the digital pathology report.

archiving at publication quality all support the pathology workflow. Several digital slides can be opened side-by-side on the monitor for comparative analysis of serial slides of a sample stained for different biomarkers. Even samples of immunohistochemistry and FISH (fluorescence in situ hybridisation) can be opened, linked and navigated alongside, which normally need consecutive steps or even separate microscopes.

Pixels making up the images have calibrated dimension, colour and intensity, features that can be used for colour separation-based automated quantification and measurements of image-objects.

Furthermore, pattern recognition of morphological and functional units within the tissue, such as glands, or hyperplastic or abnormally arranged epithelial nests, can be automatically made based on shape, size and texture identification.

Serial digital slides can also be assembled into a 3-D structure for reconstructing tissue architecture, e.g. to study tumour invasion or re-orient colorectal biopsies. Digital data, including whole digital slides with annotations and measurements, can be integrated into digital databases and shared though intra- or internet with unlimited partners, even simultaneously. The freedom to access digital slide archives for re-review, and the logistics of slide storage and sorting are simple tasks managed through a computer.

All these, of course, need advanced IT, including high speed computers, massive storage capacity, safe data handling using backup storage, and wide-range internet access and dedicated software tools with a user-friendly graphic interface.

Molecular pathology visualisation

Immunofluorescence and FISH applications and small signals detection: - Fluorescence microscopy detects fluorophores used to label molecules in cells and tissues with the techniques of molecular morphology. Fluorophores are activated at UV or visible wavelength to emit light of lower frequency, usually in blue, green or red, which can be collected through emission filters in a dark background.

Samples targeted with fluorescing labels, particularly genomic FISH, must be studied within a short timeframe to avoid false negative results due to rapid signal fading (fading artefacts).

In addition, small signals of a few hundred nm size, such as those of gene and chromosome probes in FISH, or those of its chromogenic version (CISH), are randomly placed throughout the whole 3-8 µm thickness of tissue sections, or cells, and thus some remain hidden from conventional single focus photography. These signals can only be revealed with confidence by scanning several focal planes through the sample (z-stacking, or extended focus) for proper quantification of gene/chromosome gain, such as that of HER2 on chromosome17 (CEP17) in breast cancer (Fig. 4); or for the fine spatial localisation of signals proving gene-translocations, such as that of t (9;22) resulting in the BCR-ABL gene fusion in a case of chronic myeloid leukaemia. Gene abnormalities may determine a specific diagnosis and the concomitant treatment options in an increasing number of malignant tumours.

Digital pathology within routine sign out processes

Once the digital slide scanners digitise the hematoxilin eosin, surgical pathology specimen, and then immunohistochemical second round and FISH third round slides are also available in the slide holder/server solution, a pathologist can evaluate them from the laboratory's digital workplace.

In addition to slide viewing, the software supports quantification of identified alterations. The digital report can be signed out with detailed image and quantitative data.

The world's first digital clinical path lab

The basis for a vision of digital pathology: using it must be as easy as watching television

The field is so new that the annual Digital Pathology Congress* was held for only the second time. Yet, Philips Healthcare could announce a world-first – in partnership with the Netherlands-based LabPON, the company has created the first clinical pathology laboratory to be completely converted to digital diagnosis.

'No one has written a book on how this can be done, but now it can be done and is going to help people who are still down the road deciding about digital pathology, it is going to make the journey easier for them,' said Bas Hulsken, Chief Technology Officer for Digital Pathology Solutions with Philips Group Innovation.

Dr Hulsken spoke to European Hospital during the Digital Pathology Congress, sharing his experiences with this first-ever transition of a major clinical laboratory to the digital age.

Philips and LabPON installed and deployed the IntelliSite Pathology Solution, which has CE Mark in the EU for in vitro diagnostic use and is also approved for in vitro diagnostic use in other regions including Canada, Singapore and Middle East.

'We designed a scanner for pathology that requires no interaction by the technicians,' Dr Hulsken explained. 'You load the system, you close the door, and you don't even need to press the start button. Everything runs automatically. We have made it as easy as watching television, and this is the basis for our vision of digital pathology, because if it's not that simple, then it won't happen.

'We believe in digital pathology. That, while it brings radical change, it also will bring enormous improvements over current clinical practice.' Hulsken continued. 'What we have learned is that there is not one thing that will decide the success.

'Whilst there various challenges, there are also a variety of benefits seen with the first successes, when the pathologists see improvements to their work and the business. It enhances the sharing and distribution of work. Work becomes faster, more efficient thanks to improved logistics and some features in the digital workflow that can help to speed up diagnosis, such as instant access to previous cases, side-by-side viewing of slides with different staining, measurements, counting, and annotations, as well as simplification of internal and external consults. We expect that future use of image analysis software could help pathologists to further accelerate diagnosis.

Next to efficiency, digital pathology could also improve the quality of diagnosis by enabling cross functional integration and aggregated views of a patient's clinical work-up for better informed decision making. Ultimately digital pathology will open up new ways to get more information from tissue samples. These unique insights may enable the development of predictive analytics to help further personalize patient care for complex diseases, including cancer.

Even the process of writing their experiences is part of the continuing journey for the pathology group, he added. 'They will transfer lessons from their practice and from this we will learn, so that together we will be able to further improve processes as a partner.'

Dr. Bas Hulsken is the Chief Technology Officer of Philips Digital Pathology Solutions. He received an M.Sc. in physics and an M.Sc. in biophysics from the Radboud University in Nijmegen. He received his PhD in physics from the same university, on the development and subsequent application of scanning tunneling microscopy to study chemical reactions with atomic resolution one reaction step at a time. He joined Philips corporate research in 2008 to explore the application of Philips' optical storage technology to the field of digital pathology. Four years later he joined Philips Digital Pathology Solutions as their CTO. His areas of interest include: digital microscopy, image analysis, image processing and compression, and big data analytics

* 3-4 December in London

SPECIAL: DIGITAL PATHOLOGY

25-28 May Berlin, Germany

The 13th European Congress on Digital Pathology - 2016

Originally an offshoot of telepathology, digital pathology is advancing to incorporate modern medicine with systems science, image processing, business process modelling and knowledge management. Methodological changes in microscopic techniques, imaging, molecular pathology, genetics and bioinformatics are drivers of digital pathology. The fascinating programme for the **13th European Congress on Digital Pathology (ECDP 2016)** promises insights in several new technologies.

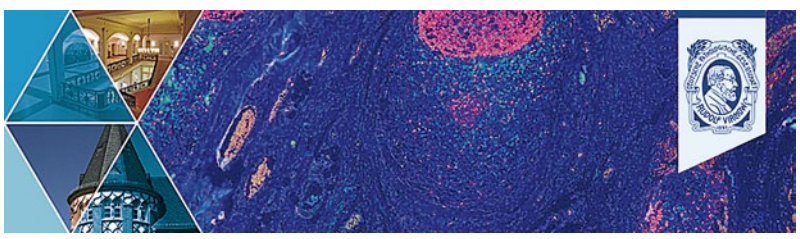
The time is now right for an overview of potentials of scanning technology and their applicability in daily practice, the organisers point out, adding a list of special sessions to note.

The 3rd International Scanner Contest (ISC) 2016 - for all slide scanner manufacturers and vendors of accompanying systems, this aims to explore the current status of scanner technology, software and integration development. Goals, methods, participants and first results will be introduced in a dedicated session.

IHE/DICOM joint meetings - The DICOM working group 26 (pathology) will discuss pathology workflow and whole-slide image management. The IHE working group Anatomic Pathology wants to integrate this standard in routine pathology processes and specifies requirements and interfaces to other standards, such as HL7. 'This joint meeting is quite important for the coordination of standard development and application. Experts from universities, hospitals, DICOM WG26 and vendors will discuss the usage of standards in pathology,' the organisers report.

Peter Hufnagl
Congress President

Klaus Kayser
Honorary President



Main congress topics

Business Processes in Pathology
- Workflow/hospital integration
- Computer aided diagnosis
- Standardisation (DICOM, HL7, IHE)
- Validation
- Quality assessment and quality management
- E-learning

Image and Data Processing
- Virtual microscopy
- Image analysis
- Imaging technology
- Label Free technologies
- Content-based image retrieval
- Knowledge formalisation and modelling

System pathology, Integrative and collaborative pathology
- Molecular pathology
- Systems biology in pathology
- Integrative pathology
- Telepathology
- Technical advances
- Bio-banking
- Bioinformatics

Interactive congress - The ECDP 2016 is featured by multiple interactive components such as ePoster (electronic poster exhibition), special hands-on workshops, dedicated round table sessions for selected topics and pecha kucha* sessions for young scientists.

* Pecha Kucha (Japanese - chit-chat) is a presentation method in which 20 slides are each shown for 20 seconds – totalling six minutes 40 seconds. This system ensures presentations become concise and fast-paced, and drives multiple-speaker events known as Pecha Kucha Nights (PKNs).

Functional neuroradiological MRI procedures

Watching the brain at work

Different sequences and contrasts already make MRI an extremely powerful imaging procedure. Through the addition of functional measuring procedures the technology really comes into its own. With the help of functional MRI it is possible to visualise perfusion patterns and metabolic activities that allow comprehensive conclusions about physiological processes. Medical physicist and Private Docent Dr Raimund Kleiser, Head of the Centre for Medical Imaging at the Wagner-Jauregg Provincial Neuropsychiatric Clinic in Linz, Austria, reports when and where functional MRI procedures are used in neuroradiology today

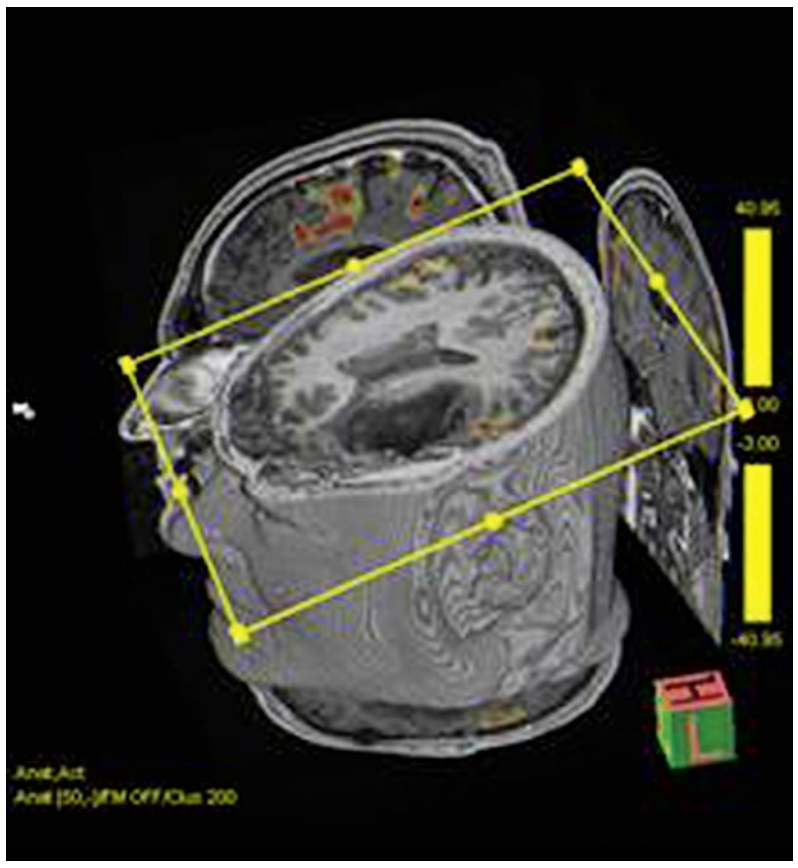
The term functional MRI (fMRI) procedures normally refers to perfusion- and diffusion-weighted imaging as well as BOLD (Blood-Oxygenation-Level Dependent) Imaging. The latter provides insights into neuronal activities in the brain by measuring O2 content in red blood cells, and is less common in clinical practice.

Measuring tissue damage from acute stroke

One neurological application that would now be unthinkable without functional MRI measurements is the diagnosis of acute stroke. Next to the standard sequences diffusion- and perfusion-weighted measurements can provide important additional information about the extent of tissue damage within minutes, which is of significant help for decisions on treatment. 'Both measurements deliver important additional information by allowing us to interrelate the respective extent of the infarction volume,' Raimund Kleiser explains. 'When the perfusion area is larger than the diffusion area, i.e. the presence of a so-called mismatch, this is a sign that perfusion in this area still works via collaterals, even though it may be delayed. In this case the tissue can possibly still be saved through the early start thrombolytic therapy, or through surgical intervention.'

Perfusion MRI is also used as a standard in neuro-oncology, where it provides additional data on physiology and haemodynamics. As higher-grade glioma show increased angiogenic activity compared to low-grade glioma, perfusion parameters enable analysts to draw improved conclusions as to the grade of malignity, patient outcome and treatment response.

'Functional imaging is also of great importance in the context of preoperative planning of tumour removal,' the medical physicist adds. 'The objective for such surgical interventions should always be to remove the tumour as comprehensively as possible without damaging important centres in the brain responsible for language, the sensorimotor system and memory. These important centres, which may be in close proximity to the tumour to be removed, can be identified and localised through the BOLD imaging procedure and avoided in a safer manner. The language centre has an exceptional position because, unlike many other centres, it is unilateral: for right-handed individuals it is located in the left half of the brain and for left-handed people it is partly unilateral in the right or the left half of the brain, and in some individual cases it is bilateral as well.'



BOLD (Blood-Oxygenation-Level Dependent) Imaging provides information about neuronal activities in the brain by measuring the oxygen content in red blood cells

Pre-surgical clarification for brain tumours is one of the most important indications for BOLD Imaging. Meanwhile, the procedure is now also being used for other neurological indications, such as the differential diagnosis of psychiatric diseases such as schizophrenia or depression. This could result in an entirely new approach to these diseases, which may even lead to improved medical understanding of their mechanisms, the expert reports: 'When it comes to treatment of these diseases, with medication in particular, we are hoping to achieve a better understanding of when and why biodynamic changes occur or not.'

Almost totally confined to scientific research so far

However, BOLD Imaging is predominantly in use in university hospitals, and even there almost exclusively for scientific research. The reason is its complexity and elaborateness. Apart from the technological prerequisites, the determination of fMRI paradigms – i.e. the conceptual formulation for the stimulation of networks – is a difficult task. The brain, says Kleiser, reacts extremely sensitively to just the smallest deviation to instructions.

'There is a difference between telling someone: "Please try to solve this task the best you can!" or: "Please try to solve this task as quickly as possible!" Completely different processes will happen in the brain.'

Communication with coma patients

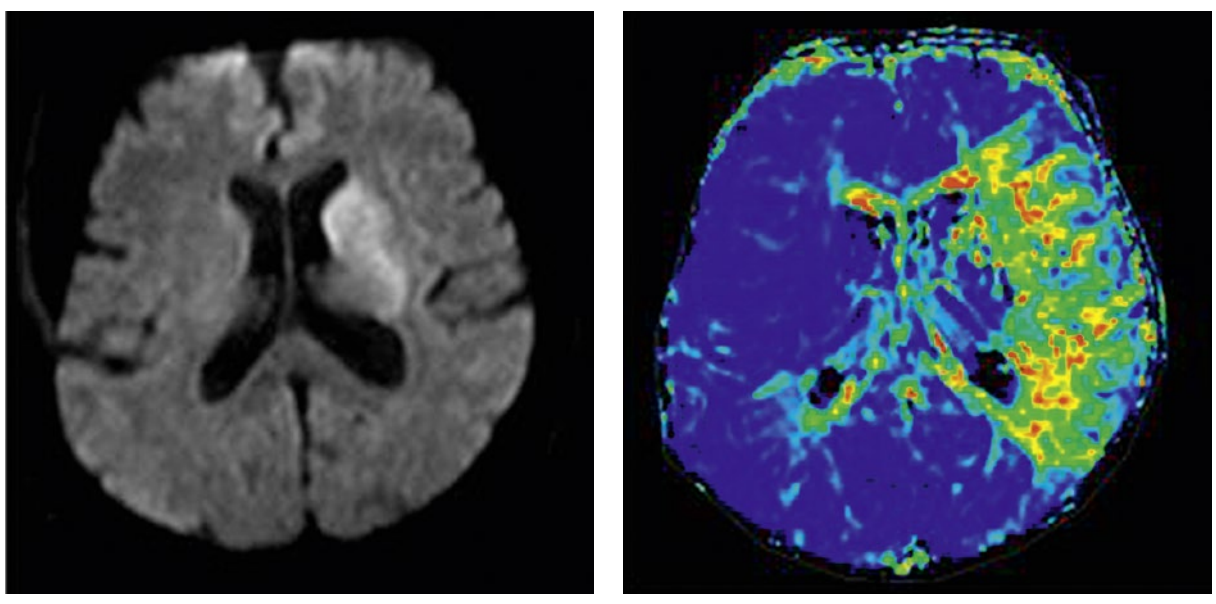
BOLD Imaging is also very time-consuming. Examining neuronal activities in certain parts of the brain, and maintaining the statistical significance, means measurements have to be repeated several times. Therefore, depending on the indication, the examination can take up to two hours – plus the time spent on evaluation of the data collected.

It is difficult to predict exactly how BOLD Imaging will continue to develop, Kleiser points out, but: 'Even now, the possibilities of what can be achieved are impressive. With the additional help of specialist software it has, for instance, even been possible to communicate with coma patients,' he reveals.

'The BOLD imaging procedure may not be of great benefit for the masses, but there are individual groups of patients for whom it will be of great benefit indeed.'

Medical physicist **Raimund Kleiser** worked at the University Hospital Düsseldorf and the University Hospital Zurich before joining the Institute for Radiology at the Wagner-Jauregg Provincial Neuropsychiatric Clinic (managed by Dr Johannes Trenkler) in 2008. In 2011, Kleiser's habilitation treatise on Experimental Radiology focused on 'Imaging of neurophysiological processes with fMRI: saccadic eye movements and clinical applications'. In 2014 he became responsible for the organisational management of the newly founded Centre for Medical Imaging at the Linz Neuropsychiatric Clinic, which combines specialist expertise from different areas of neuroscience with functional imaging.

Next to the standard sequences, within minutes diffusion- and perfusion-weighted measurements deliver important additional information about the degree of tissue damage, providing decisive assistance for treatment decisions



EUROPEAN HOSPITAL

EUROPEAN HOSPITAL Publisher,
Theodor-Althoff-Str. 45,
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Phone: +49 (0)201 87 126 850
Fax: +49 (0)201 87 126 864
E-mail: info@european-hospital.com

www.healthcare-in-europe.com

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Art Director: Olaf Skrober
Managing Editor: Sylvia Schulz
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Janka Hoppe, European Hospital,
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Representatives
China & Hongkong: Gavin Hua, Sun China Media Co, Ltd.
Phone: +86-0755-81 324 036
E-Mail: gh@european-hospital.com

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

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

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

Israel: Hannah Wizer, International Media Dep. of El-Ron Adv. & PR Co., Ltd.
Phone: +972-3-6 955 367
E-Mail: hw@european-hospital.com

South Korea: CH Park, MCI
Phone: +82 2 730 1234
E-Mail: chp@european-hospital.com

USA & Canada:
Hanna Politis, Media International
Tel: +1 301 869 66 10
E-Mail: hp@european-hospital.com

Developing digital public healthcare services in Andalucía

Europe's largest PACS project

Investment in health has been paralysed in the peninsula for the past few years, but Spain will soon have the largest picture archiving and communications system (PACS) in Europe, Mélisande Rouger reports

Accenture and Carestream are currently implementing a joint project in Andalucia, framed within the bilateral cooperation agreement between the Andalucian Health Service and the Ministry of Industry, Energy and Tourism, through Red.es for the development of digital public services in Andalucia's Public Health System.

PACS is an electronic, community-wide system that is used to capture, view, store and distribute medical imaging digitally rather than printing images onto film.

The new system will allow clinicians to manage and share diagnostic imaging data across all Andalucia's 1,600 healthcare facilities by the end of 2015. Equipment and systems will be installed in two data centres capable of storing 1.4 petabytes each, equivalent to 11,000 personal computers of 250 gigabytes. This horsepower will enable radiologists and physicians from any health facility in Andalucía to instantly access, secure and manage medical imaging studies, radiology reports and patient imaging, explained Santos Lopez, Carestream Spain Director for Healthcare IT: 'Any user anywhere can immediately access any study performed at any facility in the region. They don't need to wait at all and can access the system from their tablets and mobile phones – both IOS and Android Galaxy. This is a real progress, as doctors will be able to complement their results with patient's record and check beyond their own hospital or primary assistance centre.'


PACS supports the surgeons work in the OR

Andalucía is a giant in terms of size and population; its nearly 9 million inhabitants, about 15% of Spain's population, are spread over almost 90,000 km². The joint Carestream-Accenture initiative is expected to manage as many as eight million imaging studies, from X-ray, CT, MRI, ultrasound or any another modality, per year.

'To this day, this is the most important PACS project in all of Europe,' Lopez pointed out. 'We dare not say the whole world, but even this could be possible.'

The system will use an updated version of the Carestream Vue software, which enables image and volume reconstruction to be performed at any workstation without having to install any costly add-ons. Radiologists will be able to carry out multi-planar reconstruction and visualise any plan (coronal, sagittal, axial) independently from how or where the image was captured.


Pablo Sánchez Cassinello, Accenture Health Spain Managing Director


Santos Lopez, Carestream's Spain Director for Healthcare IT

Another novelty is the introduction of the lesion management function, which allows users to identify, segment and track a lesion in the system, to follow and monitor its evolution over time. Carestream will also be responsible for system maintenance until late 2017. Accenture, for its part, will provide the architecture of the system and its implementation, as well as user training. Up to this day, Andalucía was equipped with a series of local PACS. Using the same image digitisation system will benefit patients and professionals, and save money for the healthcare system, according to Pablo Sánchez Cassinello, Accenture Health Spain Managing Director: 'With the new PACS, maintenance costs will be reduced by 35%.' Investment in the project amounts to more than €6.7 million and is based on the previous agreement of the Ministry of Industry, Energy and Tourism, through the public corporation Red.es, with Andalucía Health Service to fulfil the objectives of the Digital Agenda for Spain within the Digital Public Services Plan and the Health and Welfare Programme. 'The initiative will be funded at 80% by Red.es, through the Regional European Development Fund (FEDER) of the European Commission, and the other 20% by the Junta of Andalucía,' Sánchez Cassinello added.

Accenture has been present in Spain for 50 years and has over 10,000 employees in the peninsula. It has worked with the Andalucía Health Service since 1998, and employs about 500 people in Malaga alone. Carestream has over 20 years experience in PACS and has been present in Spain for over 12 years. It has conducted implementations with Seville's Virgen del Rocío, the second largest institution in the country, and four health systems in Andalucía since 2005. The deal with Andalucía Health Service helped Carestream Spain to secure financial growth in 2014. However, with the general elections in October, investment has slowed down. 'We don't expect any big public competition this year,' Lopez said.

Economic considerations have prevailed in the country's public health sector over the past few years and companies have had to adapt their prices to the situation. However the worst is over, Lopez thinks: 'When you hit rock bottom the only way is up.'

Competing with multi-slice CT without the cost

Re-engineered cone beam sharpens MSK views

Although a few 3-D mini-scanners are available for a deeper view of bone joints or sports injuries, uptake has been slow, according to Andrew Hartmann, Vice President and General Manager at Carestream for Ultrasound & CT Solutions.

For difficult cases, he explained, a physician might turn to full-body CT, which is not optimised for extremity exams and not able to look at one elbow or knee.

'The implementations for orthopaedic imaging that we've seen so far have not met clinicians requirements, whether for imaging performance, costs or ease-of-use,' he explained. 'The big CTs are simply not designed to do these focused examinations. In addition, weight-bearing exams are not possible. There is additional information to be gained of the knee, ankle and feet if a 3-D image can be taken under natural load.'

Taking a fresh approach to musculoskeletal (MSK) imaging, Hartmann pointed out that Carestream has turned to a core expertise for focused-field, cone beam CT. The company offers the CS 9000 Extraoral Imaging System, used primarily for dental imaging, but the firm recently added the CS 9300 System with panoramic imaging, also used by ear-nose-throat specialists.

For a new musculoskeletal scanner, Carestream began collaboration in 2011 with Johns Hopkins University, in Baltimore, to build the first prototype of an extremity 3-D cone beam CT system from the ground up, to validate its performance with patient studies, and then to refine the system as a second-generation prototype.


Cone beam CT, a new approach to musculoskeletal (MSK) imaging

A third-generation working model was installed at the University at Buffalo, New York for extensive clinical trialling by John Marzo MD, and the orthopaedics and sports medicine department. The first European installation is scheduled for a clinic in Finland.

Smaller than the bore on a conventional CT, the opening of the prototype system is large enough to accommodate a wide range of patient sizes and obtain a reasonable volume to acquire the specific area of interest.

Carestream also opened the bore with an access door, to create a way for patients to easily step into and out of the scanner. 'If I have a bad knee, the last thing I want to do is climb into a tunnel, or to sit in a chair and slide my leg into a hole, because that way I've lost the advantage of a weight-bearing image, which is the whole point for this kind of exam,' Hartmann pointed out.

Mounted on three axes, the bore can be rotated to suit a patient position whether standing, seated or horizontal.

The prototype system has a high frame rate for exposures, and a low-dose, flat panel detector so that, rather than doing hundreds of revolutions, it needs only a single 240-degree rotation to acquire a full-field imager in one exposure, Hartmann explained.


Andrew Hartmann, Vice President and General Manager at Carestream for Ultrasound & CT Solutions

'We put a lot of effort into improving workflow,' he said, pointing to the simplified display for the user interface, and an additional patient-facing display to enhance the interaction with the system operator during an exam and to ensure a friendlier experience.

Despite its size, the OnSight 3-D can be rolled to another position, has minimal radiation shielding requirements, and needs only a standard electrical outlet to operate.

'We say this system is on target, on budget and on time because it provides imaging specifically where a physician wants to look, competes with multi -slice CTs without the cost, and lets them schedule four patients an hour while keeping the revenue stream in-house,' he said..

A prototype of this system was first introduced at the Radiological Society of North America's (RSNA) meeting in Chicago this year. After regulatory approvals, it will be branded as the Carestream OnSight 3-D Extremity System.

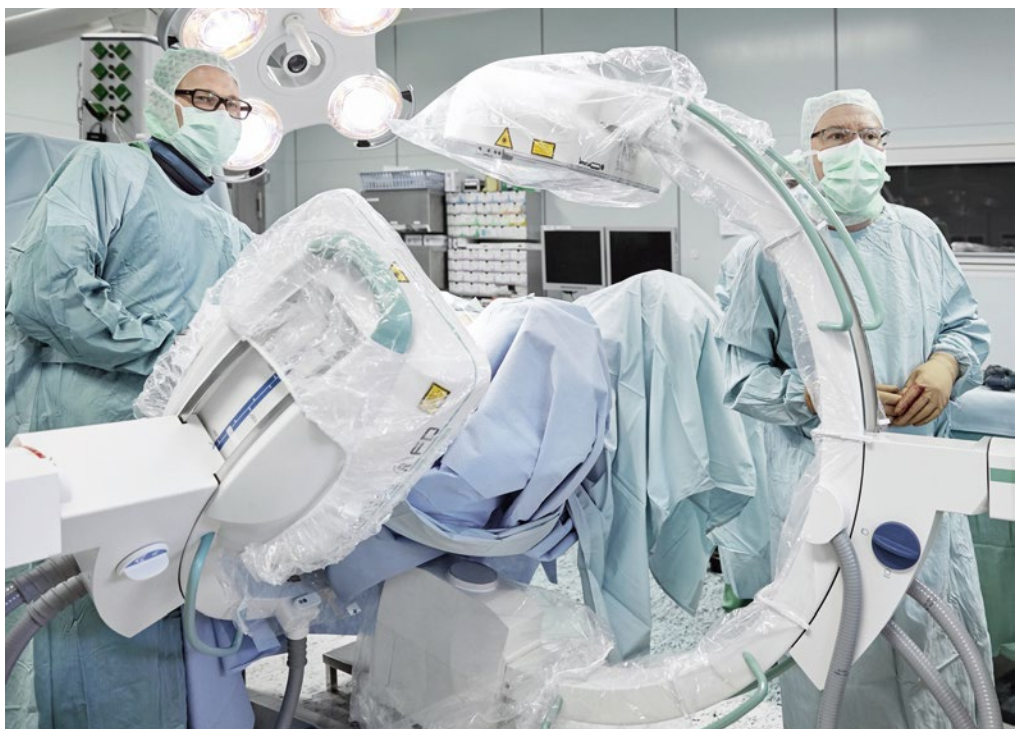
The firm plans to demonstrate this at ECR 2016 next March

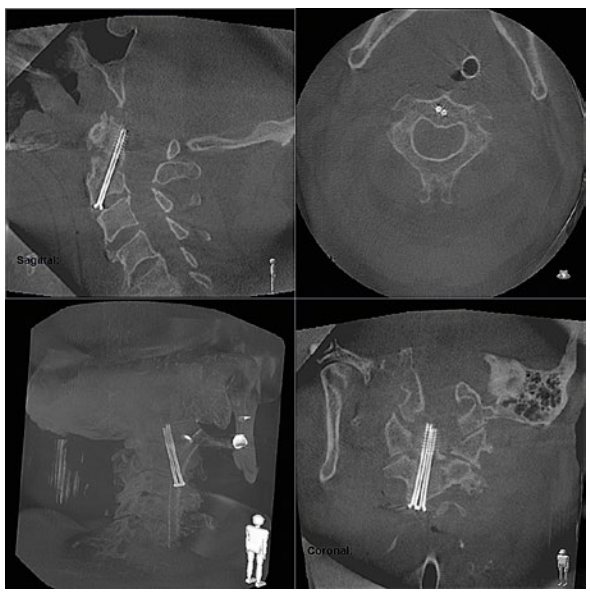
Intraoperative 3-D imaging may replace postoperative CT scans

Thumbs up for a new C-arm system

Report: Marcel Rasch

3-D imaging is continuously improving, with devices simultaneously becoming more manageable and mobile. The new C-arm system Ziehm Vision RFD 3-D is opening up a new dimension. The device was tested by Dr Jan-Sven Jarvers, orthopaedic and trauma surgery specialist at the University Hospital Leipzig, and was introduced this September during the Eurospine Congress in Copenhagen. 'In the future, newly-developed intraoperative 3-D imaging may replace postoperative CT scans and reduce the number of repeated surgical interventions significantly,' he concludes.





Intraoperative 3-D imaging: live surgery at Leipzig University Hospital. Surgeons can monitor intraoperatively how the screws are positioned

Outstanding image quality and large volume

'A big advantage,' he adds, 'is the outstanding image quality which, unlike its predecessors, facilitates a larger volume of the areas to be visualised.' With an edge length of 16cm in the scan volume, up to seven cervical vertebrae can be visualised in one scan. 'The system is of particular interest for imaging of the spine, because the area to be operated on can be assessed more clearly. Surgeons can monitor intraoperatively how the screws are positioned during fracture surgery and can change the screws if necessary or, respectively, carry on operating when the position is optimal.'

Previous image enhancers have two dimensions and miss the spine's axial view. 'This made it more difficult to assess the exact relation of the screws to the spinal canal,' Jarvers observed. Furthermore, navigated interventions mostly use CT data sets as templates. Although this facilitates a 3-D view, it means having to refer back to images taken a few days before, where the patient may also have been lying in a different position. 'Thanks to the 3-D C-arm, the patient's current situation can be assessed during navigated surgery,' Jarvers points out.

Fewer postoperative CTs and repeated interventions

Normally a hospital will carry out CT scans of the spine after surgery. However, not all hospitals adhere to this practice and some only perform postoperative CT scans in cases where the postoperative X-ray cannot be properly assessed, or if the patient develops unexpected symptoms or complications. This includes neurological symptoms such as numbness or paralysis, or increasing pain that cannot be explained. In such cases one must assume that screws are malpositioned, which could only be rectified through repeat surgery.

The intraoperative use of the three dimensional C-arm makes it possible to assess the placement of screws during surgery, lowering the risk of the need for a repeat intervention considerably.

The system also helps to assess whether the articular surface is well positioned during surgery for joint fractures. This makes the development of patients' postoperative symptoms less likely. 'You must also consider that postoperative CT scans always mean more radiation exposure and, in the case of repeated surgical interventions, also more anaesthetic administration,' he warns. Also, time and cost for the hospital cannot be underestimated. The new Ziehm Vision RFD 3-D means patient safety goes hand in hand with simplification of daily routines in the operating theatre.

Good operability and almost no limitations

'It is particularly convenient for nurses that everything is motorised,' Jarvers says. The Ziehm Vision RFD 3-D can be motorised for all four movement axes, and automatically slows down when approaching a patient and automatically stops within a defined safety zone around the patient.

'Fast processing is a further advantage,' Jarvers adds. 'Everything is very user friendly and geared towards working fast. Thanks to the large diameter of the C-arm we've had no problems with scanning, even with extremely obese patients.'

However, there can be limitations regarding image quality in patients with many endoprostheses. If surgery is carried out in the area where the cervical spine meets the thoracic spine in a patient with bilateral shoulder prostheses, those prostheses can limit image quality somewhat. 'But,' Jarvers adds, 'the images are still good enough for us to safely assess the position of the screws. The software also helps with this because it automatically blends out many of the artefacts,'

One small detail should be noted. 'The operating table should be made from carbon or at least have a carbon plate extension,' the surgeon emphasis. 'A table made from metal, or with metal on the sides, obviously makes resolution more difficult.' Other than this, Jarvers is very convinced by the image quality: 'I hope that intraoperative 3-D scans will become the standard.'

Jan-Sven Jarvers MD gained his doctorate at the orthopaedics, trauma surgery and plastic surgery clinic, at Leipzig University Hospital, where he is now a specialist in orthopaedics and trauma surgery. His involvement with 3-D imaging and 3-D navigation began in 2007. His particular focus lies on spinal surgery

Expert reviews the basics of breast elastography

Using the entire ultrasound arsenal

Although breast elastography entered clinical practice many years ago, a large number of breast radiologists are still unaware of its benefits and have not become familiar with its principles. A dedicated session during the last Spanish Breast Congress (22-24 October, Madrid) aimed to improve knowledge of this technique, by demonstrating the potential in differentiating breast lesion and diagnosing breast tumour, as well as the limitations of elastography

Report: Mélisande Rouger

'When we talk about elastography, we realise there's still a confusion surrounding its key concepts,' said Dr Sergi Ganau Macias, a senior breast radiologist at UDIAT-Parc Tauli Corporation in Sabadell, Barcelona.

Elastography was first developed about two decades ago and has been used in breast imaging quite extensively. Simply put, it aims at imaging tissue stiffness, which provides additional and clinically relevant information in a non-invasive, non-irradiating way.

Soft and flexible lesions are considered benign, whereas rigidity or stiffness is often an indicator of malignancy.

'In that sense, elastography is truly a substitute for breast palpation. The elastogram will appear next to the B-mode image and show different degrees of stiffness,' said Ganau, who has used elastography for almost a decade.

Mapping stiffness can either be estimated from the analysis of tissue strain under a stress or through shear wave imaging.

With strain elastography, which could also be called compression or static elastography, the radiologist applies the transducer and compresses the breast; the applied pressure distorts the breast and lesion to be observed. When the tissue returns to its normal place and shape, the user can assess the elastic modulus. Results are qualitative and can only be measured semi-quantitatively with different ratios or with a colour scale.

On the contrary, shear wave or transient elastography enables the user to measure and quantify lesion stiffness without compression, by assessing wave propagation.

The technique provides many benefits. It adds value to B-mode ultrasound and is particularly useful in apparently negative ultrasound studies with uncertain clinical or mammographic findings. It can also be used in case of doubt to characterise small size hypo-anechoic lesions (solid or cystic) and iso/hypo-echoic lesions (fat lobules and/or solid lesions).

Elastography can bring additional sensitivity and/or specificity to B-mode especially in type 3 or 4a lesions, and may help to monitor neoadjuvant treatment when this is not possible with magnetic resonance, or when MR is not available. Last, but not least, elastography can help to diminish axilar fine needle punction aspiration (PAAF) false negatives.

'Elastography nicely complements B-mode imaging and enables to precise indications for biopsy,' Ganau added. Some studies have shown that elastography limits recourse to biopsy and significantly reduces the number of benign breast biopsy diagnoses *(http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3558110/, Breast elastography: A literature review, A Goddi, M Bonardi and S Alessic)*.

However, despite its high specificity and slight correlation with tumoural phenotypes, the technique will never be a substitute for biopsy, Ganau emphasised.

Limitations include industry variability, as manufacturers use different nomenclature, colour charts and qualitative vs. quantitative scores. Strain elastography is also less reproducible than shear wave elastography.

'I think a significant downside with elastography is the wide variability between the different models offered by the industry. This versatility complicates the conduct of multicentre trials, which would bring vital and much needed evidence regarding elastography's indications and uses,' Ganau explained.

In addition, cut-off points remain difficult to establish in the case of shear wave elastography. 'Which one is the ideal cut-off point? When we search for sensitivity and use a low cut-off point, we will find more cancers and trigger more negative biopsies; but when we use a high cut-off point, we end up with the opposite problem, i.e. a low cancer detection rate,' he said.

False positives may be due to the presence of calcium, fibromatous component or mucinous carcinoma.

Ganau recommends using the whole ultrasound arsenal because techniques are complementary. 'It's very important to use Doppler, B-mode imaging, harmonics and elastography – in a word,' he concluded, 'everything we have to detect cancer as early as possible.'

A specialist in breast pathology and gynaecology **Sergi Ganau Macias** is a senior radiologist at UDIAT-Parc Tauli Corporation in Sabadell, Barcelona. With over a decade's experience in the use of elastography he has authored many publications and delivered many talks on this subject. He is also a spokesperson for the Spanish Society of Breast Diagnostic Imaging.

Maximising mammo on the fr

Two technologies are vying to become an adjunct for breast cancer screening to deliver conclusive diagnosis faster, John Brosky reports

Radiologists don't like to say it, but they hear themselves saying it far too often to women following a mammography exam: 'The results of the exam are inconclusive.'

Some women need to wait a week or more to receive a letter saying that results were 'incomplete,' or worse, that there were 'abnormal findings.'

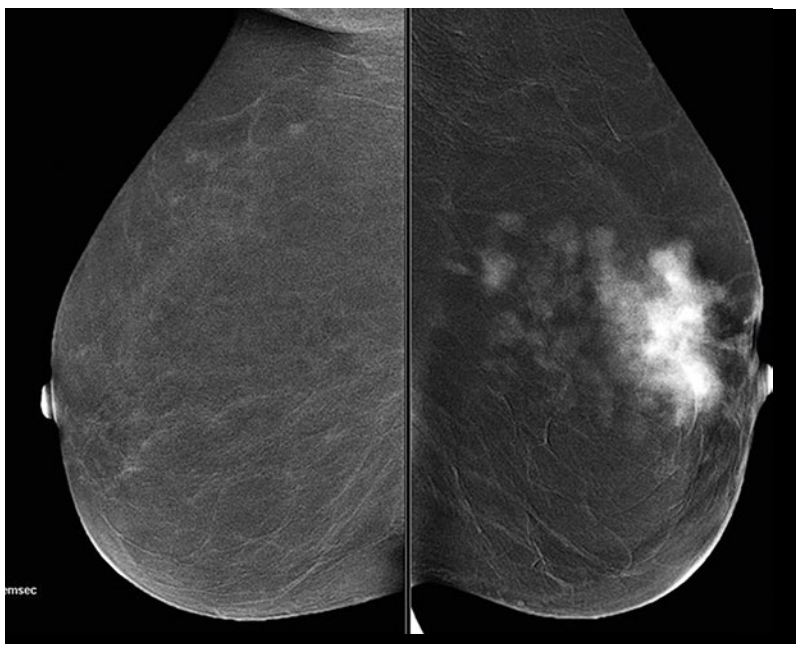
The reason so many women hear this uncertain diagnosis is that the frontline technique for breast cancer screening is an X-ray, a one-size-fits-all look at breast tissue that is based on technology going back more than 100 years.

While the chance of a woman having breast cancer today is higher than ever, and while the hope of surviving breast cancer is far better, not a lot has changed with the technology to detect cancer.

The rise of the digital age has made traditional mammograms more efficient for screening more women more often. But the sensitivity of the exam for helping the radiologist spot cancer remains at about 50 percent, which is why so many women are told their exam is inconclusive.

Thanks to advances in computer processing power and a new exam technique, two technologies have emerged, greatly improving to as high as 92 percent, the sensitivity of frontline breast screening.

This year in Paris, at the French Radiology Congress, two leading clinicians faced off to compare the results of their studies applying the two technologies for frontline mammography, digital breast tomosynthesis (DBT) and contrast-enhanced mammography, called angiomammo.



Using a traditional mammography system, angiomammography applies dual-energy exposures and an injection of a contrast agent to immediately detect cancerous tissue, seen here as a multifocal lesion that has absorbed the contrast agent.

Tomosynthesis: 'We find more cancer'

Tomosynthesis was first approved for use in Europe in 2008 and, since then, has steadily built a solid clinical case that shows it can detect 40 percent more cancers than traditional two-dimensional (2D) mammograms.

DBT captures multiple breast images, instead of just one flat image, so that algorithms can be rapidly reconstructed for a three-dimensional (3-D) view of the breast that a radiologist examines in slices as thin as half a millimetre.

In clinical studies, women who have a suspicious mass that shows up in the 2-D mammo are not sent home worrying about cancer; instead they are immediately given a 3-D tomosynthesis exam. This combination has proven to be powerful not only in detecting cancers, but also for reducing the number of call-back exams. 'In our daily practice we have fewer uncertainties, eliminate false positives and we find more cancers,' said Paris-based private cancer specialist Bruno Boyer MD.

Where there is a lesion, the tomosynthesis image situates it to aid a targeted ultrasound exam though, thanks to the greater specificity of the 3-D image, fewer echo exams are needed, Boyer added.

To this point, health insurers have been reluctant to pay for the 3-D DBT exams, calling for more studies of the cost-effectiveness. This practical issue hinders a wider clinical adoption, he pointed out, with many clinics hesitating because of the high cost of purchasing a dedicated machine for 3-D DBT exams, and the longer reading times 3-D images need.

Angiomammo: 'Diagnostic performance identical with MRI'

For the past four years, Clarisse Dromain MD has been deep in clinical research using a new technique to detect cancer that may solve the two problems posed by tomosynthesis. Angiomammo uses the same X-ray system as traditional mammography, but adds the injection of an iodine contrast agent that suddenly illuminates potentially cancerous tumours under a double-energy X-ray burst.

'Angiomammo in practice is rapid, easy to perform and can be done immediately following a standard mammogram when there are incon-

SuperSonic reveals micro vessels with AngioPLUS

Aixplorer brings new capability for detecting tumour vessels without use of contrast

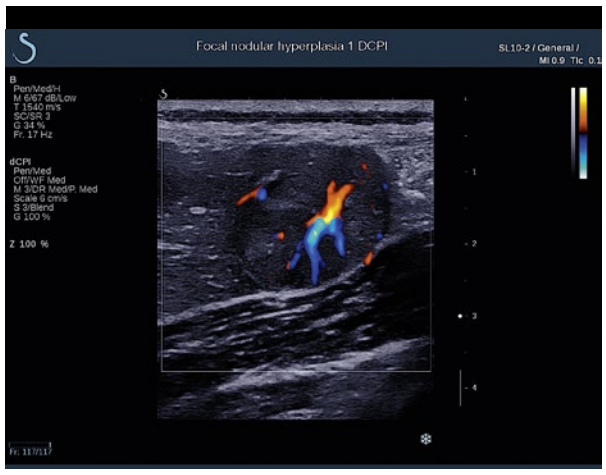
Jacques Souquet, Chief Innovation Officer of SuperSonic Imagine, and the company's co-founder

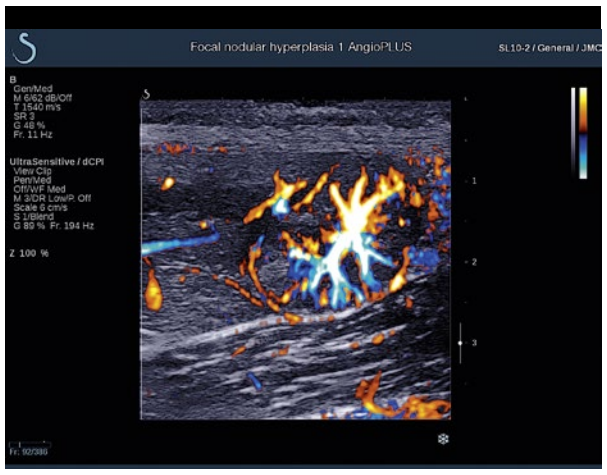
Building on an innovative ultrasound technology that continues to yield break-through capabilities, SuperSonic Imagine is introducing AngioPLUS, a third diagnostic functionality for its Aixplorer platform that promises to be instrumental in the diagnosis of cancerous tissues as well as musculoskeletal pathologies.

Previewed in October, 2015 during the French Radiology Congress, AngioPLUS will begin shipping on the Aixplorer after its global launch at the annual meeting of the Radiological Society of North America (RSNA).

'This innovation is possible thanks to the UltraFast acquisition and plane wave imaging we applied first to ShearWave Elastography for the real-time assessment of lesions, and that we extended by introducing UltraFast Doppler last year,' said Jacques Souquet, Chief Innovation Officer of SuperSonic Imagine, and the company's co-founder.

AngioPLUS leverages the capabilities of UltraFast Doppler to provide a new level of microvascular imaging for vascular evaluation. Colour sensitivity and spatial resolution are significantly improved and when combined with exceptional 2D imaging, the result is an increased detail of real-time flow information available during ultrasound diagnostic exams.





'We have improved sensitivity, compared to conventional Doppler, by a factor of 50 and this enables us to look at the microvasculature of lesions, the angiogenesis of tumours, and potentially without the use of contrast agents,' said Souquet.

According to Souquet, one of the frustrations for clinicians is that with conventional Doppler they can see the beginning of the slower flow that indicates micro vessels, but they are unable to extract the image.

'It is something that they simply can not see without enhancing the ultrasound signal using a contrast injection, and what AngioPLUS can do is to enhance that signal without contrast,' he said.

Currently the only technique for seeing micro vessels is to illuminate them with an injection of micro air bubbles into the bloodstream.

AngioPLUS may reduce the need for interrupting exams of micro vessels in order to inject a contrast agent, Souquet said, and become instrumental in aiding the diagnosis of cancerous tissues in areas such as the breast, liver, lymph nodes and thyroid as well as musculoskeletal pathologies such as inflammation in tendons.

'The advantage of our technology is the ability to use plane wave imaging on the Aixplorer. Using conventionally acquired Doppler would require a lot of filtering of their signal, looking at images sequentially, and trading off either frame rate or performance,' Souquet pointed out.

'Thanks to the UltraFast acquisition, we don't need to make this kind of compromise, and going even further, with our platform what we can do is provide a quantification of things like flow direction.'

According to Prof. Jean-Michel Correas, Vice Chairman of the Adult Radiology Department, at Necker University Hospital, Paris, 'The AngioPLUS technology significantly improves flow sensitivity in colour imaging. This innovation also enables attending physicians to quickly and accurately address challenging clinical situations, such as characterising fortuitously discovered focal liver lesions and renal blood flow disturbance.

'We believe AngioPLUS can help to avoid additional imaging or biopsy procedures.'

With Aixplorer ultrasound, the firm launched a disruptive technology for ultrasound by swapping conventional line processors for a graphics processor used by video gaming firms to create lightning-fast sonic image acquisitions.

ShearWave Elastography was the leading edge for the company to differentiate itself in the crowded ultrasound space. Progressively the company demonstrated in more than 60 peer-reviewed publications, including a multinational study of over 1,600 patients the benefits of using the ShearWave technology for the diagnosis of breast lesions.

Results showed that ShearWave Elastography, combined with conventional ultrasound criteria, allowed superior accuracy in the diagnosis of breast lesions, significantly reduced the number of false positive cases and helped reduce the number of negative biopsies.

More recently the company announced the enrollment of 2,270 patients for a milestone multi-centre study conducted in 22 locations across China to analyse the benefit of combining ShearWave evaluation of individual breast lesions to their classification using the Breast Imaging Reporting and Data System (BI-RADS) by the American College of Radiology.

In addition to breast cancer management clinical studies, over 60 liver disease-focused publications have demonstrated the reliability and effectiveness of ShearWave Elastography to assess the severity of chronic liver disease.

In April 2015, results of a 1,340 patient study confirmed the accuracy of ShearWave as a non-invasive alternative to a biopsy for staging liver fibrosis.

ontline

clusive findings,' Dromain told radiology colleagues at the Paris conference. 'What becomes interesting here is that the angiomammo exam is performed by the same radiologist without needing to schedule a later exam and without any delay.'

Working at the Institute Gustave Roussy. in Paris, in close collaboration with a research team at the Charité Hospital in Berlin, a study of 160 patients showed angiomammography had the best agreement among radiologists reading the results, which Dromain said was slightly better than inter-reader agreement with MRI and clearly better than for mammography. It also demonstrates the ease of interpreting the images from angiomammo.

Citing an Australian study, she said that patients globally preferred in a significant manner the experience of an angiomammo exam to one using an MRI scanner. A woman does not need to lie on her stomach and pass through an MRI machine, there is the absence of the noise, and a lot less patient anxiety.

Although a higher radiation exposure is needed for angiomammo, it remains significantly below levels set for screening by both American and European authorities, she said.

In her conclusion, Dromain stated that the diagnostic performance of angiomammo is very close to MRI in detecting lesions, with a sensitivity that is slightly lower and a specificity that is slightly superior to MRI, 'such that the diagnostic performance is identical'. There is not yet any study on the economics and cost-effectiveness of applying angiomammo on the frontlines of breast cancer screening, she said, and there is not a specific reimbursement, which will remain a barrier to its wider implementation in the clinic.

Breast cancer screening

Spanish experts clash over benefits and harms

Breast cancer screening has helped to detect cancer in its early stages, but it is unclear how important this contribution is to mortality reduction because treatment has greatly improved. Over-diagnosis and overtreatment remain associated risks that need to be fully assessed for screening to be of real benefit. Leading experts in this field passionately discussed these controversies in a dedicated session during the 22-24 October Spanish Breast Congress in Madrid.

Report: Mélisande Rouger

Breast cancer affects 1.7 million new people annually, including 25,000 in Spain. Incidence is high, especially among younger generations, but mortality has decreased significantly since the 1990s, making Spain the country with the lowest breast cancer mortality rate in Europe.

Part of this success is due to the implementation of a national screening programme, which invites more than five million women annually, according to Dr Marina Pollán Santamaría, investigator at the national epidemiology centre of Carlos III Health Institute in Madrid. 'Of course better treatment has helped curb cancer, but so has early diagnosis; being able to detect cancer in its early stages crucially improves outcome,' she affirmed. A vision shared by many, including Dr Nieves Ascunce Elizaga from Navarra Public Health Institute. 'The literature shows that screening decreases the risk of mortality by at least 25% in women aged between 50 and 69,' she added.

The European Screening Network (EUROSCREEN), which compiles data collected by every running screening programme in Europe, estimates that screening reduces mortality by 25 to 30% in all invited women and by up to 48% in investigated women. (Summary of the evidence of breast cancer service screening outcomes in Europe and first estimate of the benefit and harm balance sheet. EUROSCREEN Working Group. J Med Screen 2012;19 Suppl1:5–13 http://www.ncbi.nlm.nih.gov/pubmed/22972806).

The International Agency on Cancer Research (IACR) reviews all the available evidence on breast cancer (Breast-Cancer Screening — Viewpoint of the IARC Working Group. Béatrice Lauby-Secretan, PhD, Chiara Scoccianti, PhD, Dana Loomis, PhD, Lamia Benbrahim-Tallaa, PhD, Véronique Bouvard, PhD, Franca Bianchini, PhD, and Kurt Straif, MPH, MD, PhD, for the International Agency for Research on Cancer Handbook Working Group. N Engl J Med 2015; 372:2353-2358;). It recently confirmed that screening helps to reduce mortality in the 70-74 group and overall for women between 50 and 69, a group in which benefits significantly outweigh potential adverse effects, according to Ascunce. However, research has not shown any benefit for women aged between 40 and 44 yet; some experts are in favour of screening women aged between 45 and 49, but evidence is limited. Therefore screening is generally not recommended in women below 50, except those who present with a significant risk.

This precaution is well grounded: screening does have adverse effects, first and foremost false positive results. The ensuing psychological and physical damage, which may occur when unnecessary invasive examinations and surgery are carried out, cannot be undermined.

The appreciable incidence of over diagnosis has also prompted many to question screening's role and benefits.

'The worst price to pay with screening is probably to diagnose a tumour that could have receded on its own. However it's impossible to know when this happens,' Pollán pointed out.

Current estimates of over diagnosis in screening mammography vary between 0% to upwards of 30% of diagnosed cancer; contrast quality studies estimate over diagnosis to be around 6%.

These estimates are important, because over-diagnosis may lead to overtreatment, i.e. to potentially exposing healthy or not so sick women to aggressive treatments like radiotherapy or mastectomy. So the question that really matters is whether screening is worth the price to pay?

No, according to José Schneider Fontan, a professor of obstetrics & gynaecology at Valladolid University, whose talk fuelled discussions among the panel. 'Adverse effects clearly outweigh benefits. Three to four deaths are avoided for every 10,000 women subjected to screening over a ten-year period and 2.72 to 9.25 deaths are caused by overtreatment. The number of mastectomies also significantly increases with screening,' he said.

Schneider based his presentation on the work of one of the most recognised opinion leaders on breast cancer worldwide, Michael Baum, professor emeritus of surgery and visiting professor of medical humanities at University College London. Over time, Baum, a pioneer of breast cancer screening in the UK, has over time become critical of the breast cancer screening programme, arguing that women are not receiving accurate and complete information on the actual benefits and risks of the procedure. (Michael Baum: Harms from breast cancer screening outweigh benefits if death caused by treatment is included. BMJ 2013;346:f385. http://dx.doi.org/10.1136/bmj.f385).

Part of the problem with overtreatment stems from the status of carcinoma in situ, which is classified as cancer although it is a pre cancerous lesion, according to Schneider. 'It is much easier to perform mastectomy in carcinoma in situ than it is in actual carcinoma, hence the large number of interventions carried out in these patients,' he explained.

The gynaecologist also questioned the efficacy of breast cancer screening by comparing results obtained with cervix cancer screening; introduced in the 1950s, the latter translated in a drastic reduction of mortality whereas the drop has been more moderate for breast cancer screening. Causes for mortality reduction are therefore to be found elsewhere. 'The introduction of Tamoxifen and hormonal treatment in the 80s has driven down mortality, not screening. Proof for that is that mortality of prostate cancer, which is being treated in the same way as breast cancer, has decreased in equal numbers,' Schneider pointed out.

In particular, a study published in the British Medical Journal (BMJ) raised doubts about breast cancer screening (Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database, BMJ 2011;343:d4411, http://dx.doi.org/10.1136/bmj.d4411). Mortality was compared in countries of similar size, population and economic means, which practised either systematic or opportunistic screening. The authors found that mortality reduction was the same in all countries observed. 'This clearly demonstrates that mortality reduction is due to treatment, not screening. If screening worked, we would have noticed over time,' he said.

Ascunce strongly criticised this position, discarding the BMJ study on the grounds of its observational nature. She also opposed the figures mentioned by Schneider and backed up her stand with EUROSCREEN data. 'Nine deaths are avoided per 1,000 women subjected to screening over a 20-year period, during which four cases of cancer will be over diagnosed,' she said.

Optimising screening by selecting women who present with more risks and focus efforts on these patients may be a solution, according to Pollán, who offered a more nuanced view. Pollán participated in a prospective study together with the Navarra Public Health Institute breast screening programme, in which she used and recalibrated the Gail model developed in the USA. 'We found that four percent of the women observed were above the five-year risk threshold,' she said.

Researchers should also focus on prediction and especially consider breast density, which is associated with a high risk of developing cancer up to eight years after mammography and increases the risk of developing interval cancer, according to Pollán.

Nieves Ascunce Elizaga MD specialises in preventive medicine and public health, and leads the breast cancer early screening programme in Navarra. This began in 1990, after she helped to design and implement the programme, a part of the European Breast Cancer Screening Network, and several working groups on screening evaluation. A member of national and international expert committees, she has taken part in many conferences and talks, authored several screening and breast cancer publications, and is involved in several screening research projects.

José Schneider Fontan MD, professor of obstetrics & gynaecology at Valladolid University, Spain, previously held the same role at King Juan Carlos University, Madrid. He is also Research Director at the Rio Hortega University Hospital in Valladolid. After gaining his medical degree at Freiburg University in Germany in 1980 he received Spanish board certification in obstetrics & gynaecology in 1984. A PhD followed from Cantabria University in Santander in 1986 and, in 1989, German board certification in obstetrics & gynaecology from the Baden-Württemberg Federal State. His 110+ publications, on every aspect of gynaecology practice, also focus on breast cancer diagnosis and treatment.