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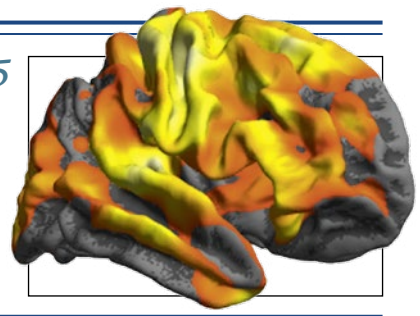

Self-help healthcare or face a penalty?

Questioning the Genetic Diagnostics Act

Report: Eva Britsch

The fact that genetic research can reveal hereditary diseases has been transferred to medical practice for some time and, since 2010, the Gene Diagnostics Act has regulated permissible DNA tests in medical diagnostics and pedigree in Germany. During a recent European Hospital interview, Professor Jochen Taupitz, Chair for Civil Law, Private International Law and Comparative Law of the Universities of Heidelberg and Mannheim in Germany, spoke of current and potential future developments in genetic diagnostics.

Precise predictions are also possible through many other medical data, such as biomarkers, and 'are becoming increasingly important in predictive diagnostics,' Taupitz pointed out. He is calling for a 'broader positioning' of this topic and sees a concrete need for regulation of somatic genetic properties. 'Both germ line and somatic mutations can be detected by examining the tumour tissue,' he explained.

Here, it is unclear whether the Gene Diagnostics Act is applicable if a germ line analysis is only carried out for comparative purposes to assess the significance of a somatic mutation. Taupitz also sees serious ambiguities in the elucidation of all genome sequencing: 'everything could come out of this,' he believes.

It was unclear whether a doctor could limit himself to 'certain groups of diseases', for example only those which are treatable. Taupitz identifies a turnaround in the distinction between diagnostic and predictive examinations that would not yet be reflected in the Genetic Diagnostics Act. Due to the increasing shift of the concept of disease to pathogenic processes and risk factors, it can hardly be 'maintained'.

The law also leaves open whether unevaluated raw sequence data should be stored for later medical questions or destroyed. Last but not least, Taupitz explains, 'After all, the GenDG is not applicable at all to the field of research, so there are numerous open questions on the border between research and the clinic!'

To know or not to know – squaring the circle

Taupitz decidedly draws attention to the fact that there will be more frequent additional findings in genetic diagnostic examinations in the future. The reason is that whole genomic analysis methods are being used increasingly in research as well as in everyday clinical practice. For physicians, this raises the question of squaring the circle, how to deal with additional findings and the right not to know in practice.

On the one hand, according to Taupitz, this knowledge could put a great strain on patients, especially if the disease is not at all treatable. But, even then there are patients who want to prepare themselves beforehand, whilst others prefer to have a carefree future. 'From a legal point of view, this is about the right to informational self-determination,' Taupitz says. The right not to know means that knowledge about the person concerned must not be 'imposed on him or her without further ado'. This results in a 'practical problem' because the physician cannot simply assume that an affected person does not want to take note of the results. Taupitz clarifies this: To be able to exercise his right not to know, the person concerned must at least know the basics of what he does not want to know – the exact communication of this knowledge could already violate his right not to know. In the field of research, the expert recommends that 'before donating biomaterials, a concrete agreement should be reached as to whether and which possible results should be communicated.'

How might all this develop? Taupitz thinks society will come under pressure to develop in citizens a stronger perception of self-responsibility – effectively to gain knowledge about one's own health predispositions and adapt one's lifestyle accordingly, or to use preventive examinations – those who do not follow this may face financial disadvantages. Therefore, Taupitz considers a penalty system in genetic diagnostics to be quite realistic, but not desirable.

Meanwhile… a long-term study raises ethical questions regarding the UK Biobank

Professor Nils Hoppe, professor of life sciences law and ethics at the Centre for Ethics and Law in the Life Sciences at the University of Hannover, is currently drawing attention to dilemmas arising from the United Kingdom's Biobank' project – a large long-term biobank study in the United Kingdom (UK) that investigates the contribution of genetic predisposition and environmental exposure (including nutrition, lifestyle, medicines, etc.) to disease development. Begun in 2006, the study volunteers will be followed for at least 30 years.

Hoppe points out that the UK Biobank cannot provide advice and support in the provision of health data. Even negative effects are possible, he foresees, such as adverse effects on insurance and employment status. 'For these reasons, the UK Biobank will generally not provide participants with health information, and a clear explanation of this policy (and the few exceptions) will be included in the participants' information material.'

The greatest challenge arises from imaging. Biobank employees are in direct contact with the participants and may already have discovered additional findings. This would give rise to a legitimate expectation on the part of the test persons. There are a number of ethical, social and legal questions (ELSI) in this project that have not yet been resolved.

Source: private

Dr Jochen Taupitz is Professor for Civil Law, Private International Law and Comparative Law at Heidelberg and Mannheim Universities in Germany, in which he is also managing director of the institute for German, European and International medical law, health legislation and bioethics. Taupitz studied law from 1973 to 1978 in Göttingen and Freiburg, gained his doctorate in 1981 and habilitation in 1988, just before he was appointed a professor in Göttingen. He is a long-term member of a great number of panels, commissions and advisory boards in the medical field.

Professor Taupitz at a workshop organised by the German Biobank Node (GBN) in Berlin in May 2018 – an event that focused specifically on the responsible use of genomic patient data

Source: Jezperfotolia.de

www.healthcare-in-europe.com

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Establishing guidelines for human/machine interactions

AI ethics and responsibilities

Report: Mark Nicholls

With Artificial Intelligence (AI) able to deliver diagnostic advances for clinicians and patients, the focus has shifted towards ensuring the technology is used in an ethical and responsible way.

As evidence emerges of a gap in research on ethical deployment of AI, Dr Gopal Ramchurn is embarking on a three-year research project that will look at setting parameters for AI usage, with a key aspect exploring the team-working approach between humans and machines and a methodology for those interactions.

'In terms of responsible AI – with software that has a human level reasoning ability – you need to be able to endow that with some level of understanding of what humans care about,' he said.

'Humans care about privacy, the meaningful use of their data and about the right choices being made on their behalf, but they also care about having control over how these choices are being made. So when you design AI that is ethical and responsible you need to factor in these aspects.'

AI expert Ramchurn, an Associate Professor in the Agents, Interaction, and Complexity Group (see profile), suggests that our understanding of these issues is currently limited. 'Therefore, it's very hard to define a standard set of principles that would help us ensure that all these levels of quality assurance are ethical and responsible,' he said.

Source: Lightspring/Shutterstock.com

Ramchurn's three-year research project will explore the team-working approach between humans and machines and a method for those interactions

Funded by a €250,000 grant from the AXA Research Fund to investigate how AI can be responsible and accountable, Ramchurn's research will focus on areas such as team-working between AI and human decision-making; where AI is deployed to support human decision-making; the extent that machine learning is deployed to make sense of insights for human decision-makers; and where computer vision algorithms identify particular features in support of human decision-making.

'There are many instances of human/machine teaming,' he explained. 'That involves some level of coordination where the human has a goal and the machine has its own goals and has to interpret what the human wants, and the other way round.

'In my new project we will look at how we develop methodology to design these interactions between humans and machines, deriving basic principles that ensure good human/machine understanding, interaction and goal setting and then establishing these design guidelines but also verifying that this methodology actually works.

'Intonation or language is very hard to understand for a machine so we need to have interaction designed – whether voice, text or app based – to engender some kind of trust between the human and the machine.'

This becomes even more critical in a healthcare setting, he said, with a need to build in safeguards in the form of explanations for why a machine is making certain decisions.

AI has already shown its proficiency in detecting cancers or heart disease, often better than doctors can, but he added: 'When it gets it wrong – even 4% of the time compared to doctors who get it 20% wrong – who do you attribute the fault to: the designer of the machine, the doctor who interpreted the data from the machine or the machine itself?'

Data used for the AI approach also needs patient's consent, and should be handled securely, he stressed.

Handling the control issue

'My goal is to develop some of the underpinning technology that will ensure AI remains safe and responsible,' he explained. 'Some of the targets will be to look at how we can design AI systems to cope with varying degrees of user understanding and how we can design interactions with AI to make sure that control is given to users when it most matters, while the complexity of decision-making is dealt with by the AI when the user does not need to be involved.' He remains concerned that medical community use of AI is still not always considering the risks.

'Healthcare involves human decision-making outside machine decision-making,' added Dr Ramchurn. 'Modelling risks around human/machine intelligence is a completely new topic and that is why we need these new methodologies to define risks.'

He will also examine how such technology can bridge the gap between health and social care – from the hospital to residential care homes and linking and sharing data held by the hospital, family doctor, and care home.

Ramchurn's research has centred on the development of intelligent software and robotic agents and how they work alongside humans and other agents. This next step will focus on the design of interactions with AI that ensures that humans have reasonable expectations about the behaviour of intelligent agents'. 'We are at a critical point in time,' he concluded, 'where key questions are being asked about how artificial intelligence will change people's lives – for better or worse.'

Dr Gopal Ramchurn is an Associate Professor at the Agents, Interaction, and Complexity Group (AIC), in the Department of Electronics and Computer Science, University of Southampton. He is also director of the newly created Centre for Machine Intelligence, and Chief Scientist for AI start-up North Star. His research interests lie in the development of autonomous agents and multi-agent systems and their application to Cyber Physical Systems (CPS) such as smart energy systems, the Internet of Things (IoT) and disaster response.

Transforming a nation's healthcare

The USA's digital revolution

Report: Cynthia E Keen

The digital revolution in healthcare in the United States is marching steadily forward, spurred by federal government regulations and financial incentives, by technological innovations, and by the necessities of increasing healthcare treatment efficiency, of lowering its cost and economic impact, and of elevating communications among providers, patients and payers to the norms of the 21st Century. The process has been slow, cumbersome, and far from complete, but much progress has been made.

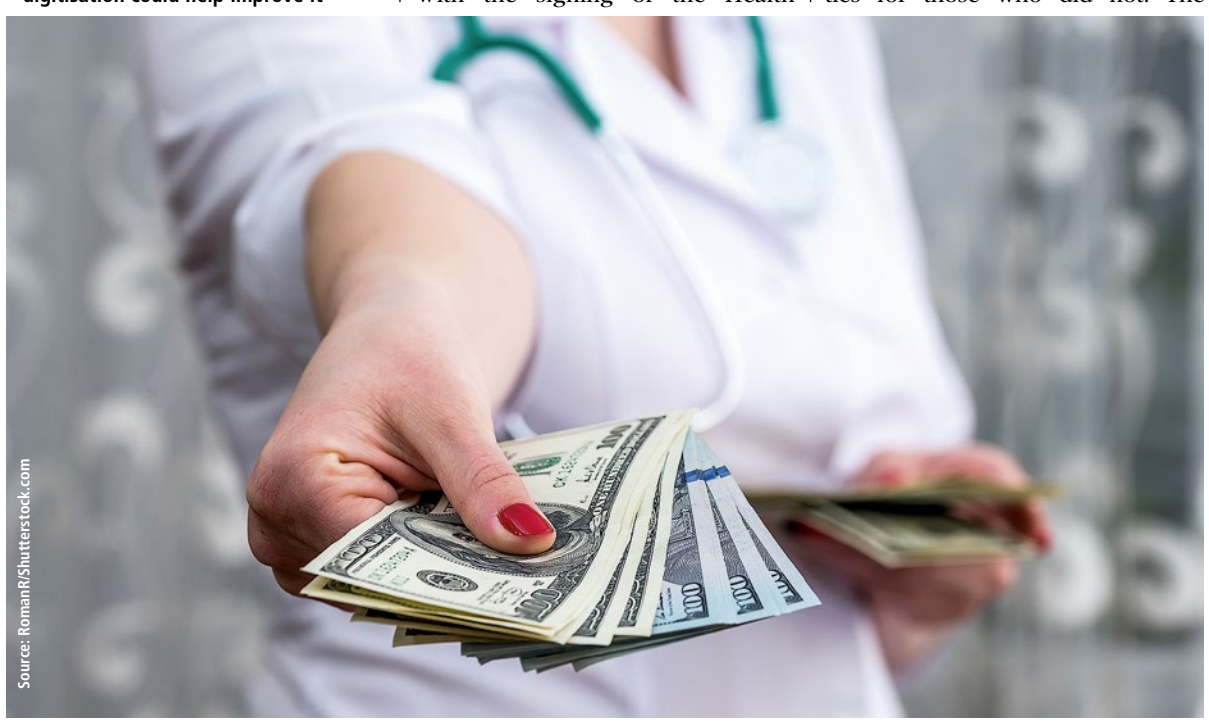
Lawrence S Friedman MD, Associate Dean for Clinical Affairs at University of California San Diego (UCSD) Health Sciences, discussed the four cornerstones responsible for the escalation of digital adoption in healthcare over the past decade in a presentation at the conhIT 2018 conference in April.

Those fundamental foundations are: federal government regulation and financial support; the need for transparent and rapidly accessible patient records; the necessity of 'big data' to quantitatively improve healthcare treatment and quality, and the transition of the USA's healthcare providers from a volume-based to a value-based economic model. These factors are reliant on the success of each other, escalating the importance and impact of digitisation, Dr Friedman explained during our European Hospital interview.

The USA's healthcare system is notorious for its costly, often ineffective and inefficient volume-based payment model – digitisation could help improve it

Federal government involvement: A 'carrot and stick' approach

With the signing of the Health Information Technology for Economic and Clinical Health (HITECH) Act of 2009, President Barak Obama changed the face of healthcare. The legislation provided financial incentives for providers to implement health information technologies and financial penalties for those who did not. The Office of the National Coordinator for Health Information Technology reports that, in 2008, only 9% of hospitals and 17% of physicians utilised an electronic health record (EHR). By 2015, this had increased to 96% of hospital and 78% of physician offices.



Source: RomanR/Shutterstock.com

Transparency of patient data

The digitisation of patient records and the integration of EMRs with specialised data acquisition systems, such as for laboratory and radiology tests, meant that, to become fully comprehensive, EHRs had to create transparency of patient data that paper-based records could never accomplish. In addition to rapidly providing clinical data to clinicians who needed it, healthcare managers could now evaluate performance criteria, treatment outcomes, and the effectiveness of quality initiatives.

Deficiencies could be identified and their impact quantified, and rectification measures could be monitored in real-time. Standard-of-care guidelines could be tracked as well as follow-through relating to treatment. And, for the first time,

Enhancing patient engagement in treatment

Blockchain technology enters hospitals

Report: Wolfgang Behrends

Blockchain is a continuously growing list of records - called blocks - that are linked and secured using cryptography. It has security elements that make it difficult for unauthorised modifications to data which is exchanged in a system that is an open distribution ledger which can record transactions between two parties efficiently and in a verifiable and permanent way.

Among those focusing on its potential is global consultancy and software development firm DataArt, which sees more healthcare organisations embracing its applications in the near future.

Denis Baranov, DataArt's blockchain expert, acknowledged it was still early days in the adoption of blockchain technology within healthcare but he feels that, over the next two years, more organisations will begin to utilise its potential as a secure and efficient way to store and share data.

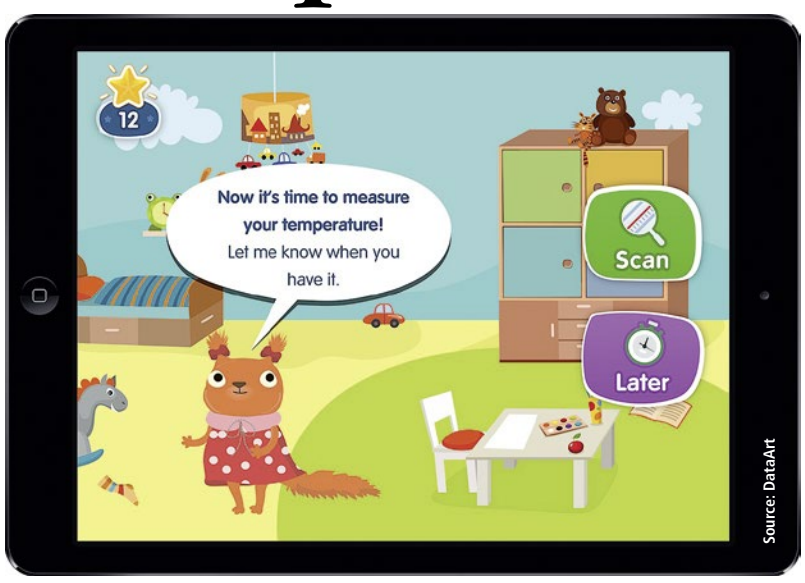
The blockchain application

As a distribution technology, he said, blockchain has an application for healthcare records, supply chain management and insurance. 'It is applicable in drugs management and supply chain management because it provides information transparency,' Baranov explained. 'The life cycle of a drug can be taken into the blockchain and customers can get information on a full history of that drug, where and how it was produced and transferred.' It can also be used to offer a full picture of a healthcare record from the hospital, patient, pharmacists and insurance providers in a secure way.

Users can share data by allowing access to a channel but restricting what information is shared. 'Blockchain is a young technology,' he added, 'but within the next year or two we will have real cases of applications in healthcare.'

DataArt also has a range of applications designed to help keep patients content and comfortable during hospital treatment by ensuring they are informed, motivated, and even entertained.

For this, the firm sells products such as gamification and patient engagement applications. It is also exploring other potential blockchain healthcare applications.



KidPRO combines aspects of professional medical software with gamification to make participation in a clinical trial rewarding

Gamification for motivation

According to Ivan Pantykin, DataArt's Delivery Manager in Healthcare and Life Sciences, gamification has a role in keeping patients – particularly younger ones – motivated during treatment or in clinical trials, using the firm's KidPRO product. Traditional ePRO (Electronic Patient-Reported Outcome) systems are often barely applicable for children, who may need adult support with it, but easy-to-use KidPRO combines aspects of professional medical software with gamification to make participation in a clinical trial fun and rewarding.

Information captured by the application is available to doctors and the study team to be used for statistical analysis through their own applications.

'Our internal research and development department's goal is to find challenges and gaps in the industry and create a concept application which can potentially cover this gap,' Pantykin said.

'We have resolved a need in clinical trials and long-term treatments to keep patients, especially children, engaged, and created a full application on an iPad for long-term clinical trials in the pharmaceutical industry, or for treatment for children with chronic conditions, such as asthma, through gamification with an animal character, which helps children stay engaged in this process.'

Monitoring and education within healthcare

As a global technology consultancy, DataArt designs, develops and supports unique software solutions across a range of sectors. Within healthcare the company focuses on technologies that will constantly monitor an individual's vital signs, detect trends and deviations, match collected data with historical records, and warn about potential problems before they present a serious threat.

To keep patients engaged in their care, DataArt created Care Companion, a device designed with multiple interfaces. For parents, or older patients, the captured data is sent to parents or carers.

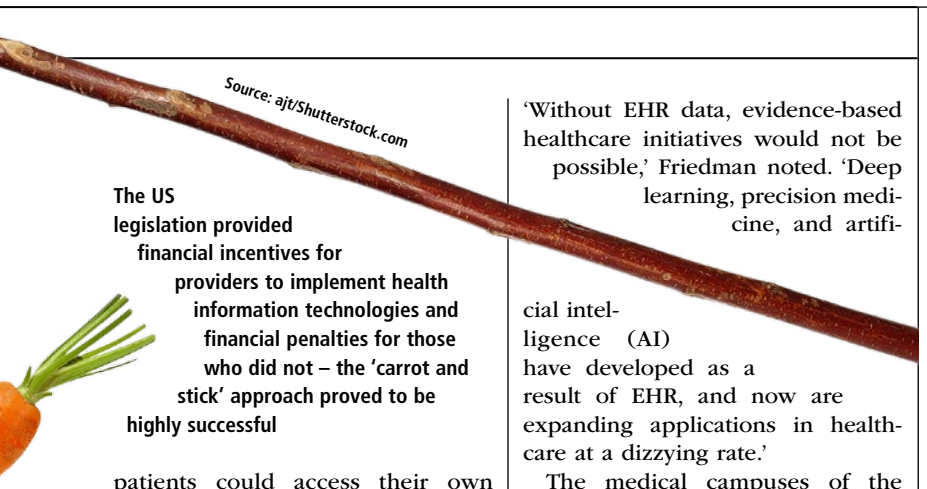
During clinical trials, patients can also use Care Companion to empower them with the tools to become more active in making care decisions.

'There are always industry discussions on how to improve the quality of patient stay in hospital and the need for applications which help patients to understand what is going on,' Pantykin pointed out. 'For example, to see where they are on the care plan, and get full information and educational material about their own medication and disease, and the particular doctors who are working with them.'

This application also extends to being able to control a patient's hospital environment, such as enabling them to adjust air conditioning or TV settings, bringing them greater independence when in care.

Denis Baranov is DataArt's Blockchain expert and Principal Consultant. He joined the company in 2008. He holds a PhD in computer science from Lomonosov Moscow State University in Russia, and has an Ms in Applied Mathematics, Informatics & Mechanics.

Ivan Pantykin is DataArt's Delivery Manager in Healthcare and Life Sciences. Before joining the firm he studied at Voronezh State Technical University in Russia.



Source: ajt/Shutterstock.com

The US legislation provided financial incentives for providers to implement health information technologies and financial penalties for those who did not – the 'carrot and stick' approach proved to be highly successful

patients could access their own medical records. These and dozens of other applications suddenly became possible and economically feasible.

'Being able to compare specific treatments with outcomes has had a major impact on mandating and monitoring improvements in healthcare quality,' Friedman said. 'As examples, both the Integrated Healthcare Association and the Office for the Patient Advocate in California track and publicly report an array of quality measures by medical group, ranking them according to performance. These reports are readily available to patients, health plans, and providers,'

Big Data/Deep Learning/AI

The acquisition and availability of data from many sources, combined with radical improvements in IT technology, have led to the utilisation of 'big data' for analysis. 'Without EHR data, evidence-based healthcare initiatives would not be possible,' Friedman noted. 'Deep learning, precision medicine, and artificial intelligence (AI) have developed as a result of EHR, and now are expanding applications in healthcare at a dizzying rate.'

The medical campuses of the University of California (UC) at San Diego, Davis, Irvine, Los Angeles, and San Francisco aggregate data. Sophisticated software analysis systems are now using deep learning/AI to identify the best treatment outcomes for patients with specific diseases/conditions – and drilling deeper – specific symptoms. These initiatives may be in their earliest stages, but Friedman expects the technology to revolutionise evidence-based individualised medical care, making the work of a physician more accurate and efficient – and less costly.

Volume- to value-based financial compensation

The USA's healthcare system is notorious for its costly, often ineffective and inefficient volume-based payment model. The accountable care mandate imposed by the federal government is forcing a change to value-based care. Put simply, instead of being paid for the number of treatments and services performed, providers are being incentivised to keep patients healthy and out of physician offices and hospitals.

Quality of treatment is now being prioritised over quantity of treatments. With digitisation, the performance of providers can be compared to any standard. The national goal is to reduce healthcare costs while improving the health of a nation and while optimising its healthcare-related resources.

Dr Lawrence S Friedman is a professor of medicine and the associate dean for clinical affairs at University of California San Diego (UCSD). A primary care paediatric specialist, he was one of four physicians involved in the evaluation and implementation of the hospital's EHR system. He also led the initiative to establish a state-wide telemedicine program for patients and providers and is an enthusiast about promoting how digitisation can transform healthcare.

The EFLM Strategic Conference

Placing the medical lab in a future landscape


Source: Gorodenkoff/Shutterstock.com

The need to ensure that laboratory medicine can meet the future challenges of a rapidly changing healthcare environment sits at the core of an innovative strategic conference for this sector.

The agenda of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Strategic Conference in Mannheim (18-19 June) highlighted the challenges, and also outlined areas of discussion to enable laboratory medicine to adapt and evolve to take advantage of what technology and innovation offers for the future.

Inspired by the REM song 'It's the end of the world as we know it', the theme for the conference was, 'The end of laboratory medicine as we know it?' That provocative title was, explained EFLM President Michael Neumaier, designed to stimulate debate and seek a strategy to ensure medical laboratories can take a significant role in future healthcare, as well as to consider the disruptive impact of on-going digitisation of technologies and a digitised society.

Virtual reality, big data and automation are changing laboratory practice

How can the sector learn from other industries? How does it respond to the scenario where comprehensive data usage is now in the hands of patients (as the sovereign of their data) as well as healthcare professionals? The aim of such questions, Neumaier said, was to look at where the sector will be in a decade's time in the light of recent advances such as smart phones and mobile apps.

'All these generate data that can be integrated into health systems and health plans in terms of prevention, prediction and personalised medicine, but origin, commutability and quality of these data often will not be transparent to doctors,' he pointed out.

'Laboratory medicine plays a role in some 70% of medical decisions, but with these changes in analytical platforms, distribution of data and digitised medicine we have to look at where the place for the laboratory could be?'

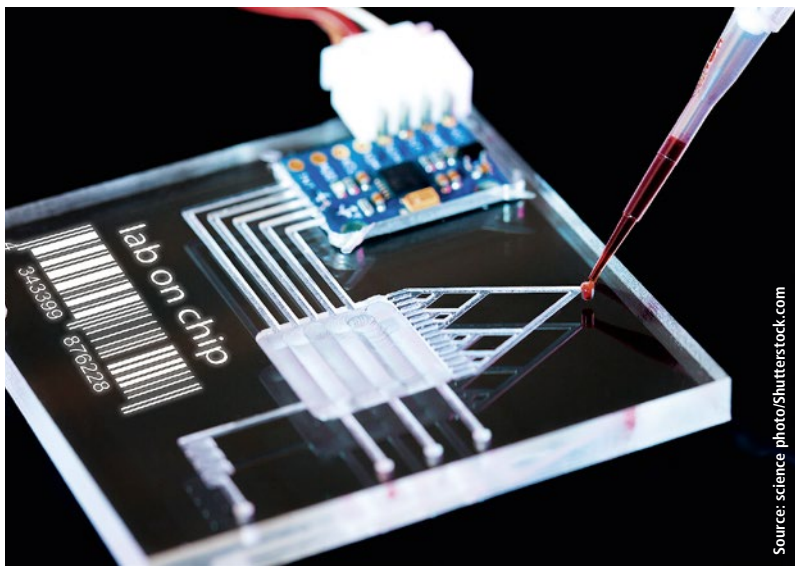
Focus on disruptive developments

The key sessions in the programme were designed to help medical laboratories respond with speakers looking at disruptive technologies in laboratory analytics; investigating disruption through biomedical informatics technologies (big data for prediction and architectures of present and future information technologies); the challenge of integrating laboratory and clinical data; and how to communicate complex information to the patient.

With the in-vitro diagnostic industry already looking around eight years ahead to new technologies, the conference brought in high-ranking speakers from major companies to offer ideas on how the medical laboratory can be more forward-looking.

With the move away from the classic central laboratory towards the patient using miniaturised labs, Neumaier said, and storage of microfluidics and implantables that provide data, the sector is entering a world where more data is generated beyond the traditional laboratory.

New devices, such as miniaturised labs, are being adopted quickly



Source: science photo/Shutterstock.com

'We are seeing these rapid changes with digitisation and disruption events applying to basically everything, not only medicine, of course, but medicine has been very reluctant and now is a last big resource that is facing digitisation challenges.'

He pointed to 'Industry 4.0' and the current trend of automation and data exchange in manufacturing technologies, but suggested that, whilst industry is moving fast, medicine has been slower to adapt and react and must catch up.

Social media leads patients to ask different questions

A key session examined patient empowerment and the relationship a patient may have with a specialist in future laboratory medicine through, for example, internet data and smartphone apps and more often liaising directly with medical laboratory personnel over results. 'Patients may now be asking different questions, after consulting their patient peer groups through social media,' he pointed out. 'For example, they might ask questions they have not asked their physicians before, so we have to know how to respond to ensure patients receive good advice.'

In an IT technology session, discussion centred on data information and biomedical informatics, which he believes will need much closer

Transmission of bodily fluids inevitably presents a serious danger

'Any needlestick injury is one too

'With Vacuette safety products you can minimise the risk of contamination and injury,' the manufacturer Greiner Bio-One reports. 'Needlestick injuries from contaminated puncture devices are the most common source of infection for diseases transmitted by blood or other bodily fluids and are still among the most common occupational accidents today. This is a serious danger!

'Doctors are the most affected by this risk, the activities with highest risk are primarily venous and capillary blood sampling. Today, many pathogens have been identified that can be transmitted via blood. HBV, HCV and HIV pose the greatest dangers.

'Studies also show that significantly more infected persons are found among hospital patients than in the "normal population". Preventive measures, such as the use of a safety product and employee training, can significantly reduce needlestick injuries.'

Vacuette safety products offer protection against potential needlestick accidents

With the topic of safety is gaining increasing importance in healthcare, Greiner Bio-One reports that it wants to offer customers the safest possible conditions for daily work with patients. 'For many years Preanalytics has been developing a range of different safety products to reduce the risk of contamination and needlestick injuries,' the company continues. 'The first safety products were launched at the turn of the millennium.

'Vacuette safety blood collection sets are particularly suitable for blood collection from the patients with difficult veins. They are available in different needle sizes and tubing lengths. An integrated safety mechanism that is already activated in the patient's vein provides even greater safety in the blood collection process. Greiner Bio-One offers reliable protection against potential injury risks with these innovative safety solutions.'


Source: Greiner Bio-One GmbH

Another example, Vacuette CLIX Safety Hypodermic Needle, is equipped with a protective shield for the cannula. Immediately after blood collection, this shield is folded over the cannula and the needle is securely enclosed. A possible needlestick injury can thus be effectively counteracted.

'Customer feedback is important to the company, which is why it is part of the development of our products. Through on-going research and development, our company is constantly launching new and improved sample collection products for clinics, hospitals,

Professor Michael Neumaier is chair for Clinical Chemistry and Laboratory Medicine in Mannheim Medical Faculty at Heidelberg University, Germany. He has been a member of its Faculty Board since 2013, when he also became Dean of Studies, serving until 2015, and then Deputy Dean. Between 2013-15 he was also President of the German Society for Clinical Chemistry. In January 2018 he became President of the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM).

cooperation between the lab and clinical side. 'If we want to define ourselves as a profession that's in medicine, and not only an analytical technical profession, then we must go more into medical dialogue.'

Harmonising education to equalise quality

Preparing the future generation of laboratory specialists to be ready to compete in this environment is key and, within this, the EFLM endeavoured to create common training frameworks to harmonise education to create the same quality across Europe and facilitate movement of practitioners between countries.

The Mannheim event is the second EFLM strategic conference – the first was in 2014.

How does Neumaier assess medical laboratory readiness for looming challenges? 'That is very difficult,' he conceded, 'I don't think anybody has a clear cut solution for the problem, but the consensus is that things will change.'

The hope is that the conference helped to position lab medicine to deal with future healthcare advances and see laboratorians play an increased role in patient care.

Diagnostics lobby calls for simplification

Registration hurdles must be overcome

The need to do more to combat resistance in Germany was keenly emphasised by delegates at the VDGH (The German Diagnostics Industry Association) event held in Berlin this May. Only the answer, or at least the common will, is missing to bring this threat under control via a concerted concept, reports European Hospital correspondent Eva Britsch.

Matthias Borst, Chairman of the Board of the German Association of the Diagnostics Industry, lists the figures like a prayer wheel: Every year as many as 700,000 people die of antimicrobial resistance – each case also generates additional general public costs of €10,000. Antimicrobial resistance is a global problem. Three-quarters of medical practitioners worldwide have already experienced antibiotic failure. The reasons include excessive use in countries such as the USA, where antibiotics are taken like candy.

Politics lags behind

Borst stressed that resistance must be prevented at an early stage. The development of rapid testing is progressing, politics lags behind. Specifically, this is about the inclusion of new diagnostics in standard care in German statutory health insurance (GKV).

The inclusion of new diagnostics, and thus their reimbursement via the Uniform Value Scale (EBM), must be faster and more transparent. According to Borst, doctors must have the certainty that their laboratory budget will not be overstretched by the use of tests.

A lot of money is also involved in this issue, and the interests of the association that springs from the interests of its member companies must not be ignored.

Of course, Borst praises the German government's initiative in 2015, for which it submitted its own antibiotic resistance strategy in DART 2020. The 20 most important industrialised and emerging countries had also put the topic on the agenda.

Source: Henning Schacht

Matthias Borst has served as Chairman of the Board of the German Association of the Diagnostics Industry since 2010

Source: Henning Schacht

Professor Klaus Heeg MD is the Medical Director of the Department of Infectious Diseases, Microbiology and Hygiene at Heidelberg University Hospital

The VDGH panel openly communicated that it was not a matter of defeating resistances, but merely 'keeping them in check' – it was a misconception that rapid tests could solve everything.

Unnecessary antibiotics prescriptions

Other worrying figures: Professor Klaus Heeg MD, Medical Director of the Department of Infectious Diseases, Microbiology and Hygiene at Heidelberg University Hospital, emphasised that, in Germany, ninety percent of antibiotics are prescribed by general practitioners (GPs) and only ten percent in hospitals – eighty to ninety percent of antibiotics are unnecessary. The bottom line is: costs to the general public and increasing resistance from misdirected drugs.

The problem is that many patients demand antibiotics from their physicians and the latter can hardly escape the pressure applied by the 'customer' patient.

This lies among the reasons why there is currently a project developed by the National Association of Statutory Health Insurance Physicians (KBV) and the Association of Health Insurance Funds (vdek). Intended to support prescribing physicians in out-patient care to provide a far more targeted treatment of acute respiratory tract infections, this project will receive a €14 million grant from the Innovation Fund.

Results are expected to be presented in 2020. It remains to be hoped that this money will not trickle away again in the general formation of resistance.

o many'

laboratories, medical practices and blood transfusion services. Perfect functionality, maximum safety and high product quality are ensured. For this reason, customers have been placing their trust in Greiner Bio-One for many decades.'

In addition, new products are currently in the research, development and test phase. In 2019 a new and evolutionary safety product will be marketed.

Headquartered in Kremsmünster, Austria, Greiner Bio-One International GmbH focuses on preanalytics, life science, diagnostics and OEM. The extensive product portfolio for routine and special applications in pre- and post-analysis ranges from evacuated blood collection tubes, urine tubes and containers to many other safety and accessory products as well as BSG (erythrocyte sedimentation rate), transport and disposal containers, as well as various auxiliary devices such as decappers. Details: www.gbo.com

'*Why not take a risk?*' belief boosts antibiotic overuse

Antibiotics are mostly prescribed for acute respiratory infections (ARIs), yet most of these infections are viral. A new study shows that inappropriate antibiotics prescriptions are widespread, contributing dangerously helping antibiotic-resistant organisms to grow. Overuse could be due to attitudes among patients and clinicians, current George Washington University research suggests.

Understanding prescribing practices is important which is why a group of scientists led by Fiona P. Havers, MD, from the Centers for Disease Control and Prevention in Atlanta, Georgia, USA, designed a study to analyse out-patient antibiotic prescribing for ARIs during influenza seasons and to find targets to improve antibiotic stewardship.

The cohort vestudy enrolled outpatients aged six months or older with ARI evaluated at out-patient clinics associated with fi US Influenza Vaccine Effectiveness Network sites during 2013-2014 and 2014-2015 influenza seasons. All patients had influenza tests. Antibiotic prescriptions, medical history, and diagnosis codes were collected from medical and pharmacy records, as were group A streptococcal (GAS) testing results in a patient subset.

The researchers found that antibiotics were likely prescribed inappropriately to a great number of the 14,987 out-patients in the study who presented with symptoms of a broadly defined ARI characterised by cough. Among all those prescribed antibiotics, 41% lacked a diagnosis code for which antibiotic therapy is potentially indicated. Most suffered viral upper respiratory tract infections and bronchitis. Those with influenza confirmed through research testing accounted for a substantial proportion (17%) of all antibiotics prescribed, yet fewer than a third of laboratory-confirmed influenza patients were given a clinical diagnosis of influenza.

The results strengthen the call for improved antibiotic stewardship. Increased efforts are needed to support adherence to prescription guidelines and improved point-of-care influenza diagnostics and recognition. Increased access to sensitive and timely virus diagnostic tests, particularly for influenza, could reduce unnecessary use.

However, the USA's George Washington University research suggests there is another rooted problem in over prescription: a 'Why not take a risk?' mentality is widespread among patients and care providers.

Improve communication

Led by David Broniatowski, assistant professor in George Washington University's engineering management and systems engineering department, the study analysed patients' and cAnlinicians' perceptions of antibiotic prescribing for upper respiratory infections in acute care. They surveyed clinicians and patients from two large urban academic hospital emergency departments (EDs) and a sample of nonpatient subjects regarding their bottom-line understanding of information about antibiotics according to fuzzy trace theory, as well as relevant knowledge and expectations.

While clinicians demonstrated greater knowledge of antibiotics and concern about side effects than patients, the predominant categorical gist for patients and clinicians was 'why not take a risk,' which compares the status quo of remaining sick to the possibility of benefit from antibiotics. Many knew antibiotics do not work against viruses, yet the providers still believed the antibiotics might help patients feel better. Side effects from antibiotics were often thought essentially nil for the individual patient, Broniatowski said. 'Unfortunately, this individually rational action leads to negative consequences for society.'

Thus communication strategies directed at patients and providers are needed, along with sensitive testing and guideline adherence, to reduce inappropriate prescribing.

Meeting the challenge of modern laboratory demands

Utilisation Management Tools bring benefits

Faced with the constant challenge of increasing demand and a backdrop of falling reimbursement, the Mayo Clinic in the USA has adopted an innovative and proactive approach to managing its laboratory services. This has seen the US-based medical giant embrace a variety of tools and reference materials to aid clinician decision making, improve care and lower costs.

During the FiLM 2018 – Frontiers in Laboratory Medicine January conference in Birmingham, United Kingdom, Dr Curt Hanson, Chief Medical Officer of Mayo Medical Laboratories at Mayo Clinic, Rochester, outlined the organisation's approach, including procedures implemented to guide appropriate test ordering and education packages.

For an organisation such as the Mayo Clinic, which conducts 25 million tests annually, it is important to achieve value based care, Curt Hanson believes

A key element lay in harnessing big data to help better inform the testing profile of Mayo Clinic, while continuing to cost-effectively meet the needs of clinicians and patients.

It was ever more important to achieve value based care, he said, particularly in an organisation such as the Mayo Clinic, which conducts 25 million tests annually; but he stressed there were multiple components to consider.

'To add value, you must move beyond thinking about cost effectiveness and think about clinical effectiveness. You have to think about the impact it has in terms of confidence in patient care.'

Big data can help to evaluate test effectiveness

In his presentation – Demand utilisation – the Mayo Clinic approach – he said big data was critical in understanding populations. However, he warned: 'We have to remember that databases are not necessarily designed for our purposes but getting access to them can really help us to move towards understanding value in the lab.' With tests such as ESR v. CRP, for example, big data can highlight information that can help work out the relative value of such tests. 'It gives an opportunity to look at routine tests and an opportunity to flush out waste from the system,' Hanson said. It can also look at test usage and effectiveness to work out internal guidelines on testing, and see what savings can be made. He pointed to Clinical Decision Support Tools and Utilisation Management Tools, used by the Mayo Clinic, and effective in other settings, as having clear benefits but stressed the importance of laboratorians knowing how to use these tools. CDS tools can support frequency of tests, cost information, value-based testing, where there should be restriction on tests, and population health data, Hanson explained. Utilisation Management Tools can provide clinician education, help decisions, make certain tests obsolete, restrict frequency of certain tests, review admission and treatment templates, look at physician profiling and report cards and establish a utilisation review process for the send-outs.

Dr Curt Hanson, Chief Medical Officer of Mayo Medical Laboratories at Mayo Clinic, Rochester, USA, is a haematopathologist with a research focus on chronic lymphocytic leukaemia (CLL) and the myeloproliferative neoplasms (MPN). He has played a key role in the development of novel flow cytometry assays to detect minimal residual disease in CLL and the application of laboratory-based prognostic risk factors. Hanson is also a Consultant and Vice Chair (Extramural Laboratory Affairs) in the Division of Haematopathology, Department of Laboratory Medicine and Pathology at Mayo Clinic.

Laboratory strategies need clinical input

Hanson also pointed out that using genetic counsellors to review high cost hereditary testing was a good move and that 'genetic counsellors more than prove themselves in terms of value'. From a philosophical challenge perspective with clinical laboratory utilisation, he warned that laboratorians must be 'comfortable with degrees of uncertainty'.

'I believe that, as laboratorians, we need to lead the way with utilisation management. We have tonnes of data, let us use that to reduce that waste,' he said.

'In addition, as laboratorians we must get out of the office and think clinically,' Hanson added. 'We have to think differently on how value-based laboratory strategies can contribute to patient care and use big data and analytics to help drive laboratory-based initiatives.'

The International Consensus Conference on Patien

Patient groups should be preci

Report: Anja Behringer

Although blood transfusion today is a well-established and safe procedure, the medical science community has not yet arrived at a consensus regarding appropriate PMB methods. 'Many PBM approaches have not yet been scientifically validated; consequently over- as well as under-transfusion might be associated with adverse events and complications for the patient,' explained Dr Erhard Seifried, Medical Director and Medical Managing Director of the blood donation services of the German Red Cross and professor for transfusion medicine and immunohaematology at Frankfurt/Main University Hospital.

Seifried chaired an international conference in Frankfurt that aimed to clarify the relevance of blood transfusions and establish alternative treatments for anaemia. However, it was impossible to define a set of precise standards. The 200 participating experts from 40 countries and five continents were flabbergasted.

Systematic transfusions

Blood transfusions are needed ad hoc when accidents or surgeries cause severe blood loss or, on a regular basis, for patients suffering inherited blood cell disorders such as sickle cell anaemia or thalassaemia, or cancers such as leukaemia, or myelodysplastic syndrome (MDS). Moreover, external factors e.g. lack of iron or vitamins, radiation for cancer therapy, or certain types of medication, can negatively affect blood cell formation.

To date there is not a single study on preventive blood transfusions

Appropriate blood management and determining the correct volume of blood to be administered requires complex preparatory exams. However, actual treatment methods vary widely from country to country – this much was ascertained during the ICC-PBM conference.

Professor Dr Reinhard Burger, immunologist and Director of the Robert Koch Institute in Berlin from 2010-15, was somewhat exasperated when speaking with our EH correspondent: 'Nothing is clear, there are no comprehensive studies and only a small percentage of existing studies can be analysed.' 1,500 studies were evaluated for the issues addressed by the consensus conference, but a mere 142 met modern evidence standards and could be drawn upon as a basis for discussion. The experts' idea: to evaluate the data scientifically and objectively determine the best possible treatment for each individual patient. This turned out to be an impossible task.

Blood counts of older and chronically ill patients established prior to surgery often show anomalies, which means more and larger volumes of banked blood are needed. Since pre-operative anaemia is considered a risk factor during surgery

Predictive potential of Big Data in the lab

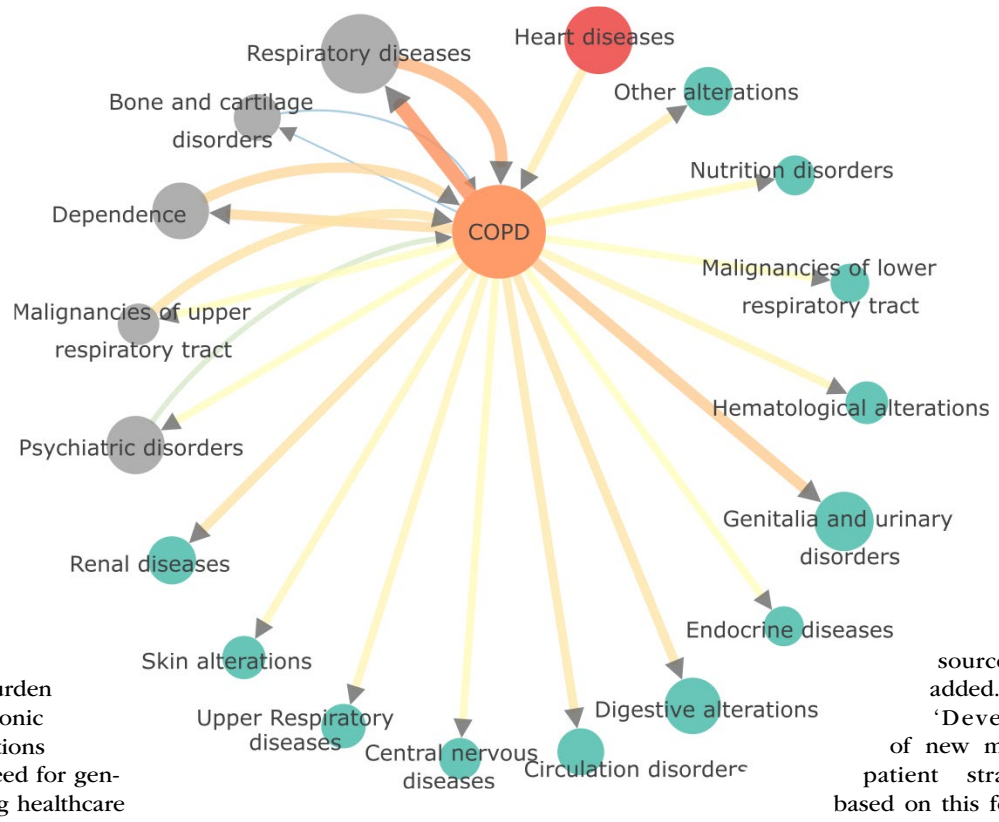
Big Data can be a critical tool in helping clinicians develop advanced patient health risk assessment and stratification models as well as leading to a new level of patient empowerment, reports Mark Nicholls

Professor Josep Roca outlined the benefits of Big Data in a laboratory context during the European Federation of Clinical Chemistry and Laboratory Medicine (EFLM) Strategic Conference held in Mannheim, Germany, this June. Under the heading 'Big Data for prediction in the lab', he discussed how disruption through biomedical informatics technologies and how using Big data for prediction is bringing about paradigm changes for diagnostics.

Stressing the importance of health systems relying on health-related date and analytical tools, he told European Hospital: 'An ideal healthcare setting should facilitate an optimal support to care decisions and delivery by reducing the complexity of the massive amount of multi-disciplinary data being produced every day and should improve efficiency of health outcomes both in terms of well-being and expenditures. 'Such a health system relies on the availability of health-related data and analytics tools.'

During the session, Roca – Professor of Medicine at the University of Barcelona and senior consultant at Hospital Clínic of Barcelona – analysed the three forces currently driving profound healthcare transformations:

- changes in biomedical knowledge
- the burden of chronic conditions
- the need for generating healthcare efficiencies.



Comorbidity Network diagram for elderly COPD in the Catalan population, 2018
Source: Ákos Tényi

Accelerating scientific evidence transfer to practice

Roca also addressed the role of data science in the current health scenario, as well as opportunities and barriers we are facing for adoption of big data analytics in health. Roca and team have been using Big Data to collect data for projections on the healthcare impact of chronic obstructive pulmonary disease (COPD) over the next 15 years (see diagram).

Enhanced clinical predictive modelling, he said, and personalised diagnostic and treatment tools – such as clinical decision support systems and patient decision support systems – can contribute to the acceleration of transfer of scientific evidence to practice, helping in the identification of gaps in care and in targeting interventions to the most appropriate sub-populations of patients. 'Overall, the unique potential of information from health data within a digital health framework is the enhanced extraction/generation of novel knowledge through the integration of multiple information sources,' Roca added.

'Development of new models for patient stratification based on this foundation would help to define the most appropriate action plan for patients, supporting the vision of personalised healthcare. Moreover, deployment of big data analytics in an integrated care setting should contribute to patient empowerment through efficient patient decision support systems.'

Finding a proper strategy

In terms of clinical outcome, the potential of Big Data is that it can support healthcare professionals in the development of patient health risk assessment and stratification models, integrating health information from informal care, formal healthcare and biomedical research, while creating new knowledge on disease mechanisms.

In turn, Roca suggests, this will generate healthcare efficiencies and facilitate patient empowerment provided that an appropriate implementation setting is achieved.

However, he notes that barriers and opportunities to enable the potential of Big Data applications in health have been reported recently in several publications.

His view is that four strategic areas need to be addressed to face these current challenges: cloud-based tools and services; enhanced clinical predictive modelling; implementation and evaluation; and governance and regulatory aspects.

His conclusion: 'A proper implementation strategy, tackling privacy and regulatory constraints, would highly contribute to enhance healthcare outcomes and patient experience of care while reducing costs and improving the health of populations.'

Josep Roca MD is Professor of Medicine at the University of Barcelona, senior consultant at Hospital Clínic of Barcelona and senior researcher at IDIBAPS in Spain, as well as Adjunct Professor at the University of Southern Denmark (Odense). He is the author of more than 300 original articles in peer-reviewed journals and several book chapters, review articles and books. His two main interests are chronic patients management (integrated care and systems medicine) and gas exchange and skeletal muscle bioenergetics in chronic patients.

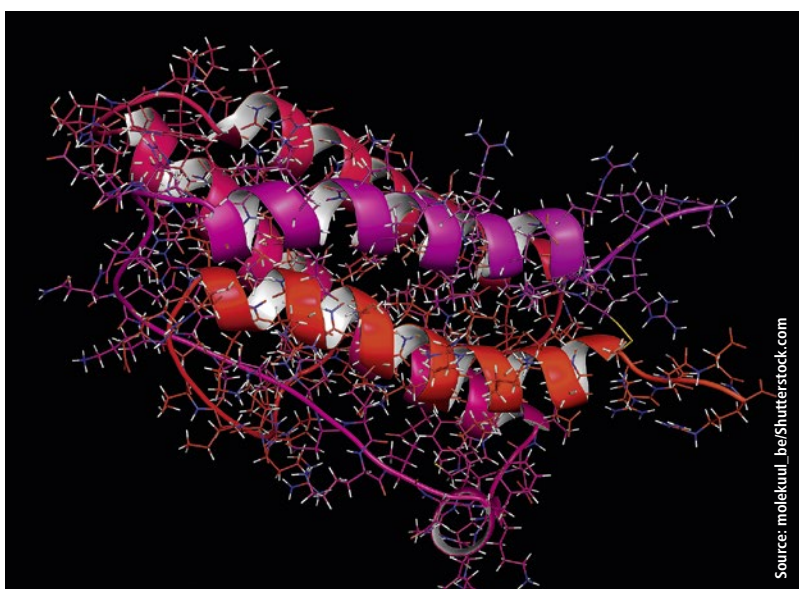
nt Blood Management

isely defined

associated with increased mortality, myocardial infarction, stroke and kidney diseases, it was suggested that anaemic patients be identified prior to surgery in order to stimulate own blood cell formation. One way to do this is the administration of iron and erythropoietin – known as EPO – or a combination of both.

The advantages and disadvantages of these substances compared to conventional procedures have not yet been scientifically ascertained since such a therapy is not without risks. Intravenous administration of iron can exacerbate infections and cause allergic reactions, while the manufacturers of erythropoietin point out a number of possible adverse events such as thrombosis, as Professor Seifried reported.

Administration of erythropoietin (3-D rendering) could stimulate own blood cell formation in the anaemic patient before surgery


Source: molekuul_be/Shutterstock.com

The International Consensus Conference on Patient Blood Management (ICC-PBM) aims for a transparent and scientific approach and international cooperation. This is very much a joint event, supported by the American Association of Blood Banks (AABB), the International Society of Blood Transfusion (ISBT), the German Society of Transfusion Medicine and Immunohaematology (DGTI), the French Society of Blood Transfusion (SFTS), the Società Italiana di Medicina Trasfusionale e Immunoematologia (SIMTI), the European Blood Alliance (EBA) and the Centre of Evidence-Based Practice (CEBaP).
ICC-PBM is also supported by the Australian Red Cross Blood Service (ARCBS), Canadian Blood Services (CBS), International Collaboration for Transfusion Medicine Guidelines (ICTMG), International Society on Thrombosis and Haemostasis (ISTH), National Blood Authority (NBA), and the EU Directorate General Health.

Anaemia patients need individual evaluation

Whilst the analysed studies did not provide sufficient data to clearly correlate preoperative anaemia and complications such as stroke, myocardial infarction and kidney disease, the experts did arrive at a unanimous conclusion: prior to surgery anaemic patients should be identified. However, anaemia treatment must be decided on a case-by-case basis. The experts recommend a decision algorithm that includes factors such as age, co-morbidities, haemoglobin concentration, duration of anaemia and type of surgery. 'When treating anaemia pre-operatively, each patient needs to be evaluated individually since spontaneous anaemia requires a very different approach than long-term iron deficiency.

'Moreover, in older patients treatment is more urgent than in younger ones,' Seifried explained. Thus, the decision to administer iron, erythropoietin or a combination of both, depends on numerous factors.

The experts agreed on a second point. To date there is not a single study on preventive blood transfusions. Consequently, no recommendation can be issued at this point. The ICC-PBM conference, Burger said, did provide pointers and possible new approaches for future studies.

The conference discussions also showed that a low haemoglobin concentration is not a sufficient indicator for treatment. According to the World Health organisation (WHO) anaemia is present with a haemoglobin concentration of <12 g/dl in women and <13 g/dl in men.

'These values were defined fifty years ago and are based on data from five studies – today this is not conclusive evidence,' Seifried pointed out.

Adding to this, Burger said: 'Patient groups must be defined more precisely and be viewed in a more differentiated way. After all, we treat the human being, not the haemoglobin concentration.'


Source: Schnartendorff – RKI

The President of the Robert Koch Institute, **Dr Reinhard Burger**, was formerly head of the Department for Immunology as well as the Department for Infectious Diseases. He gained his PhD (1976) and habilitation (1982) at the Institute for Medical Microbiology, Mainz University and, between 1983-87 was professor for immunology at the Faculty for Theoretical Medicine in Heidelberg University, Germany. In 1989, Burger joined the Free University of Berlin (University Hospital Benjamin Franklin) as professor for immunology. He has also been a visiting scientist in the National Institutes of Health in Bethesda, MD, USA, Harvard Medical School, Boston, USA, and the Medical University in Wuhan, China. In 1993 Burger became chairman of the National Advisory Committee on Blood at the German Federal Ministry for Health.

LC/MS research and routine use

LC/MS, i.e. the combination of liquid chromatography (LC) with mass spectrometry (MS) – an analytical method developed primarily for environmental analysis and live science – remains a keen topic in the medical laboratory. In recent European Hospital issues, we have outlined various reasons why this procedure is in increasingly popular in the medical lab. Here we continue with an interview held at the clinical-chemical laboratory in the Institute for Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics (ILM) at Leipzig University Hospital. For the last eight years, Professor Uta Ceglarek and colleagues have been working on a procedure to utilise the gold standard, mass spectrometry, for steroid hormone analysis in patient care – and the last two years brought success.

Report: Walter Depner

WD: LC/MS combinations were recognised as relevant for the medical lab 40-50 years ago. Why has it taken so long for the procedure to become established?

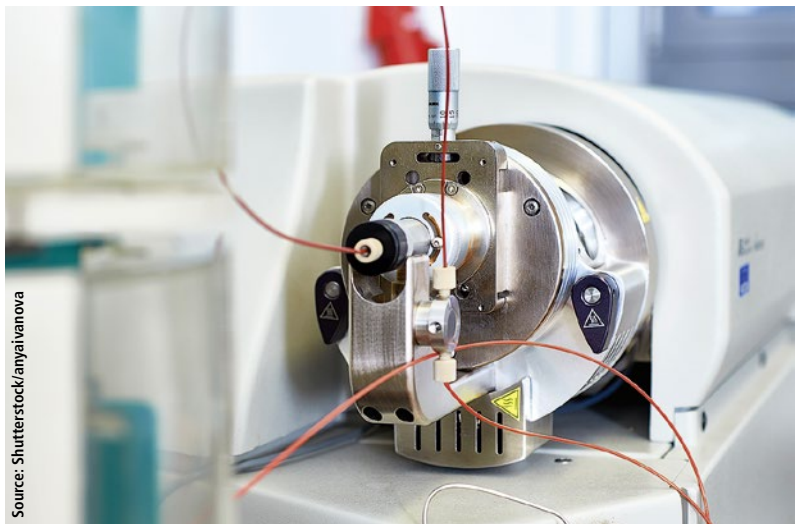
Uta Ceglarek: 'In the last century its use in the clinical laboratory was limited to the combination of gas chromatography and mass spectrometry. The combination of LC with mass spectrometry was initially a big challenge because it required a high vacuum for the separation of ions in a mass spectrometer, as well as needing eluents with high flow rates for the LC. It was only the development of atmospheric pressure ionisation, for which the Nobel Prize was awarded in 2002, which paved the way for LC-MS in routine use.'

How did Leipzig's 12-strong working group grow so big?

'You need to differentiate between two things here. For the last 15 years my research focus has been on the development of methods to analyse metabolites and proteins based on LC-MS/MS. I'm currently working on this with 12 scientific and medical doctoral candidates.

'We've been using LC-MS/MS at the ILM seven days a week in clinical routine since 2000. It is primarily being used for newborn screening, TDM, toxicology and steroid analytics. We have nine technicians in this department.

'We have already mentioned the development of a gold standard for steroid hormone analytics in patient care.



Source: Shutterstock/anyaivanova

Closeup of a mass spectrometer in the research laboratory at the Centre for Molecular Biomedicine (CMB) based in Jena, Germany.

What is the main advantage of this method, bearing in mind that hormones could be "measured", anyway?

'LC-MS/MS is often referred to as a gold standard. However, it also depends on the quality of the method developed. Our objective was the development of a routine method for the simultaneous analysis of all relevant steroid hormones. The advantage compared to the immunoassay is the same as for TDM: the use of a smaller sample volume, no cross-reactivity and simultaneous analysis.'

Who mainly benefits (clinics, departments) from this in the hospital and what is the benefit in individual cases?

'We receive samples from the University Hospital Leipzig but also from endocrinological practices beyond the hospital. The benefit lies, without a doubt, in diagnosis, which is based on a reliable method of determination.'

Of your two large groups, one is for research and one for routine. Are the members working at full capacity by carrying out routine laboratory analyses, although these are not quite comparable to other lab procedures? Do they carry out research in other areas?

'We've partnered many scientific projects at Leipzig University Hospital, as well as with national and international partnerships on metabolome and proteome research for different diseases.'

Are there other classes of substance apart from steroid hormones that the group is looking at, and what about validation, or accreditation respectively?

'We have mainly examined lipid metabolism and bioactive lipids in body fluids and tissue. This also includes methods to examine eicosanoid metabolism, cholesterol homeostasis or apolipoprotein metabolism.'

All the methods and procedures mentioned need significant expenditure on devices and systems, i.e. hardware and software. How big are these factors financially and in the number of staff members needed?

'The development and validation of LC-MS/MS procedures for clinical routine diagnosis requires special scientific expertise, but equally creates a scientific advantage. The operation of LC-MS/MS systems in clinical routine is only possible with specialist technical staff because these systems are highly complex to maintain and run in daily routine. Thus 24-hour availability of the systems is difficult. 'At the moment, there are technical developments offered by various commercial providers aimed at improving the robustness and ease of operation for routine laboratories. The acquisition costs of a mass spectrometer depend on the specifications required. However, they are now comparable to the investments needed for classic laboratory analysers. Increasing availability of commercial IVD test kits will could further improve the availability of LC-MS/MS technology in clinical routine.'

Professor Uta Ceglarek is Assistant Director at the Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics (ILM) at University Hospital Leipzig, where she has headed the newborn screening laboratory since 2005. After gaining her degree in chemistry and doctorate in analytical chemistry, Ceglarek specialised in toxicology and clinical chemistry. In 2010 she wrote her habilitation on clinical metabolome research. From 2000 she has been working to develop mass spectrometry diagnosis for newborn screening, therapeutic drug monitoring and metabolism. She is a member of the board at the German Society for Newborn Screening (DGNS) and a spokesperson for the Clinical Mass Spectrometry section at the German Society of Clinical Chemistry and Laboratory Medicine (DGKL).

In recent years, how has the device industry developed in the creation, or further development, of devices/systems for medical diagnostics, and what do you use in your laboratory?

'As mentioned, the industry has definitely acknowledged the need for robust LC-MS/MS analysers for routine diagnosis. The availability of routine test kits has specifically contributed towards the increasing use of LC-MS/MS technology.

'Our laboratory is equipped with different LC-MS/MS systems used for medical care (routine diagnostics) as well as research. Development and validation of these systems takes time and requires specific scientific expertise, but at the same time this creates a scientific advantage.'

Increasing productivity and throughput

Liquid chromatography-mass s

Liquid chromatography-mass spectrometry (LC/MS) has become a highly valued procedure in state-of-the-art laboratories – among them the Dr. Wisplinghoff Laboratory in Cologne, which adopted the method a decade ago.

In its forty years, the organisation has provided physicians with the entire clinically relevant analysis spectrum of laboratory medicine, pathology, transfusion medicine as well as human genetics, and employs more than forty specialists in these fields. 'We support our practicing colleagues through valid findings so that they can provide optimum care,' the laboratory's founder Dr Uta Wisplinghoff points out.

When European Hospital correspondent Walter Depner interviewed chemist Dr Lars Kröner, who leads the department of clinical and forensic toxicology and drug analysis at Dr. Wisplinghoff, he spoke of the company's involvement with and future applications of LC/MS.

EH: In a hospital lab, the team knows the structures of the institution, its departments and facilities. While even in such a setting you never know which and how many samples will arrive on any given day, you do have an idea about the volume and the type of work your lab will face. In a non-hospital lab the situation is entirely different: with thousands of clients, you never know what you have to expect. Does this make your daily work more difficult?

LK: No. While there are seasonal variations we are well prepared for anything that comes in.

How do you manage pre-analytics – a critical workflow component? Do you have fixed time slots when you accept orders or do you react spontaneously and flexibly?

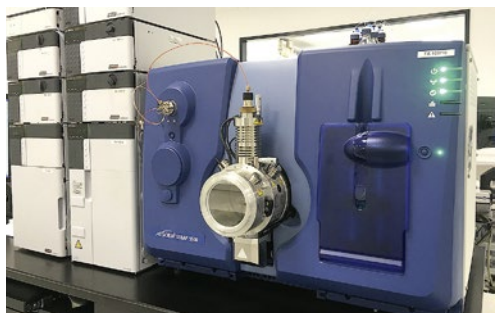
'At this point we do not provide a 24/7 LC/MS service,' Kröner pointed out. 'Pre-analytics is largely defined by the stability of the analyte. Cooled samples are analysed upon arrival. Emergency tests, such as examining urine samples for drugs, and samples with time-critical parameters, such as immunosuppressants, or amiodarone, or drug tests in capillary blood or urine in substitution patients are handled as soon as possible and definitely on the same day.

The method was first introduced at Dr. Wisplinghoff Laboratory a decade ago in 2008

LC/MS plays a significant part in easing the daily workload

When did you begin to use LC/MS in your lab and what is its value?

'We introduced LC/MS in our lab in



Heard at the 14th ECDP in Helsinki

Sometimes AI can outperform experts

Machine learning is adding a new dimension to pathology and already outperforming experts during some tasks, according to several speakers at the 14th European Congress on Digital Pathology (ECDP) who revealed up-to-date developments.

However, whilst AI is set to herald a new future for digital pathology, Johan Lundin, associated professor for biomedical informatics and research director at the Institute for Molecular Medicine Finland (FIMM), is concerned that digitisation of equipment is not evolving quickly enough to benefit from what machine learning already offers.

Lundin confessed, when speaking with our European Hospital correspondent after the conference in Helsinki, Finland: 'It was really exciting. Somehow the whole spirit has changed because of the use of artificial intelligence in the form of machine learning for pathology – maybe that's the reason for the high numbers attending.'


Source: Norman Zerbe

Participants at the joint 14th European Congress on Digital Pathology and 5th Nordic Symposium on Digital Pathology in Helsinki, llate May into June 2018

Held jointly with the fifth Nordic Symposium of Digital Pathology, the event (May 29-1 June) attracted 375 delegates, almost double the number expected, from 33 different countries with 74 speakers. Drawn together were researchers, pathologists, clinicians and industry with a theme of digital diagnostics and intelligence augmentation and a focus on AI for pathology.

'A substantial part of the talks included AI or deep learning/machine learning, so it has really grown rapidly,' Lundin added. There are obvious reasons – not just the hype with AI but also the proof that has appeared during the last two years that machine learning-based approaches can really deliver.'

Among the conference organisers, Lundin pointed out projects in which AI now replicates or even outperforms what experienced experts do in areas such as detection of rare events, and isolated cancer cells among millions of normal cells in lymph node samples.

A prognostic heatmap based on outcome-supervised deep learning in a series of breast cancer tissue microarray samples

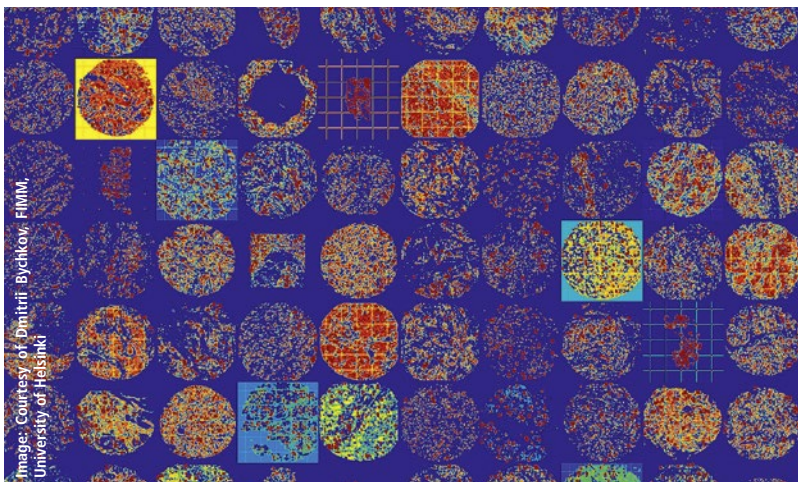


Image: Courtesy of Dmitrii Bychkov, FIMM, University of Helsinki

His research group has been involved in a project where a diagnosis can be made directly from an image for risk prediction without involving a pathologist. 'We showed that we can train a classifier, for example in colorectal cancer, with images of tissue and then have patient outcome as an endpoint in the AI training process, so that we can predict the outcome of patients directly from the images,' he said. 'The algorithm has no actual knowledge of the disease, it just learns the patterns of images, but can outperform experienced pathologists in predicting patient outcome.'

However, he added that one of the issues when applying deep learning in digital pathology is the importance of having good ground truth, because those currently set by pathologists tend to be subjective with low levels of agreement in the profession.

'Ground truth and end points are important,' he continued. 'So we should try to predict those end points that are easier to establish, for example if the patient has survived a cancer or not; or whether the patient responds to a treatment instead of trying to replicate classifications performed by a subjective human observer.'

Among ECDP keynote speakers was Greg Corrado, Director of Augmented Intelligence Research at Google Brain, who discussed AI within pathology and raised some of these key issues, while Professor Harry B Burke stressed that, despite the advances AI offers, clinicians should remember the important goals are improved quality, efficiency and safety of healthcare.


Source: Kai Lindqvist

Dr Johan Lundin is Research Director at the Institute for Molecular Medicine Finland (FIMM), whiDch is part of the Helsinki Institute for Life Science (HiLIFE) at the University of Helsinki, where he is also Associate Professor in Biomedical Informatics. His key research focus is on digital technologies and artificial intelligence to improve diagnostics and personalise care. Lundin is co-founder of Aiforia (formerly Fimmic), a FIMM spin-off company developing a cloud-based platform for AI-supported digital diagnostics within pathology.

Lundin believes AI is already playing an important role in digital pathology. 'We've seen it in so many fields already, especially when we start to achieve what has been called superhuman performance, when you start to see this application when an algorithm actually outperforms a highly-trained expert then you know that this will create a big change. Then the question is just how quickly will it happen?

'It needs validation studies, but I'm already sensing that a change has happened in attitudes and that pathologists now really understand what the promise is. It's not going to take their job, but will be something really powerful to make healthcare more efficient, offer performance with higher quality and also better safety.'

Lundin is, however, less enthusiastic about advances in digital pathology equipment.

'I have not seen the same big change as in the algorithm side, you can see some improvements but not on the same level as with the machine learning and AI,' he said.

'I hope that the AI applications can be a driver and motivation for better equipment and instruments, because it's extremely important to have a good quality image to apply all these algorithms.'

In Finland, several institutions are acquiring better scanners and he is liaising with manufacturers to drive this forward in a broader sense. He referred to Grundium, a start-up company in Finland that has developed a whole slide scanner instrument, designed to be AI enabled.

Additionally, a new event at the conference was the 'ESDIP Digital Diagnostics Award' for which innovators and companies pitched their innovations and received feedback from a panel of experts on stage. Ten finalists from start-ups, established companies, researchers and pathologists presented innovations in digital diagnostics for pathology. The winner was Dr Andrew Janowczyk, from Case Western Reserve University in Cleveland, USA, with HistoQC: A quality control pipeline for digital pathology slides.

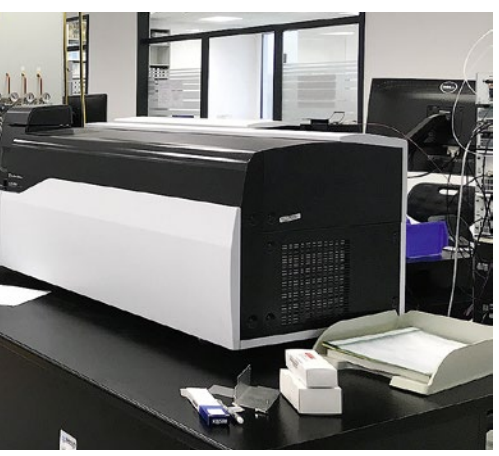
Despite the scarce advances in equipment, Lundin concluded: 'These are exciting times for digital pathology with AI and there was a really positive feeling about it during the whole conference.' ■

spectrometry

2008, pretty much exactly ten years ago. From the very beginning we developed our own methods, primarily in the context of psychopharmaceuticals and drug abuse. Later, we also included hormones and metabolic products.

'The added value is, above all, that we can offer new kinds of analyses, which previously we had to out-

Currently used by the lab for forensic and clinical purposes, LC/MS primarily detects active ingredients in medication, hormones and drugs



source,' he explained.

'Since we have been using HPLC-UV/VIS methods and ELISA tests with LC/MS we have recorded improved precision and an increase in throughput. Moreover, our own developments reduce price per piece as compared to commercially available kits and assays.'

In your lab, which samples or analyses are most frequent?

'This is clearly the detection of hormones such as calcifediol and steroids, but also TDM and drugs from capillary blood, blood, serum, urine and hair. With regard to LC/MS/MS at this point we solely use triple quads, two of them as hybrids with a linear ion trap, Otrap.

',The ion trap allows us to obtain structural information even in low concentrations. Triple quads offer high sensitivity and a larger dynamic range for exact quantification, while being tolerant in terms of matrix interferences.

'Short analysis cycles enable high sample throughput.'

Which MS methods, such as sector field, quadropole or TOF, does your lab use?

'Tandem mass spectrometry with triple quad and single quad with ICP-MS and GC-MS.'

Which instrument configurations do you use?

'For LC/MS/MS we work with Sciex and Shimadzu, i.e. normally four pumps for online extraction; for GC-MS and GC-MS/MS we use Shimadzu, for ICP-MS we use Perkin Elmer.

Which parameters does you lab determine today with LC/MS and what are your plans for the future?

'Currently we use LC/MS primarily to detect active ingredients in medication such as psychopharmaceuticals, antiepileptic medication or immunosuppressants; hormones such as calcifediol and steroids; and drugs, both for forensic and clinical purposes from capillary blood, blood, serum, urine and hair.

'Interesting future parameters concern pharmaceuticals where a closer TDM, i.e. minimum blocking level, might be advantageous, for example in antibiotics; other areas are biomarkers, for example with regard to the thyroid, but also drugs in alternative samples. Sputum and breathing air might also be possible.

'Last, but not least, there is forensic toxicology – to diagnose driving ability, for example. Our lab is leading in terms of capillary blood.'

How did the research team handle the transition to this more chemical/technical system of working?

'No problem at all; the team received the usual LC/MS training. Some colleagues were also trained in areas such as equipment maintenance or development and validation of methods.' ■

Following graduation, chemist **Dr Lars Kröner** became a research assistant in the forensic toxicology departments of Bonn and Cologne forensic medicine institutes. In 2008, he was appointed head of the department of clinical and forensic toxicology and drug analysis at the Dr. Wisplinghoff Laboratory in Cologne, Germany.

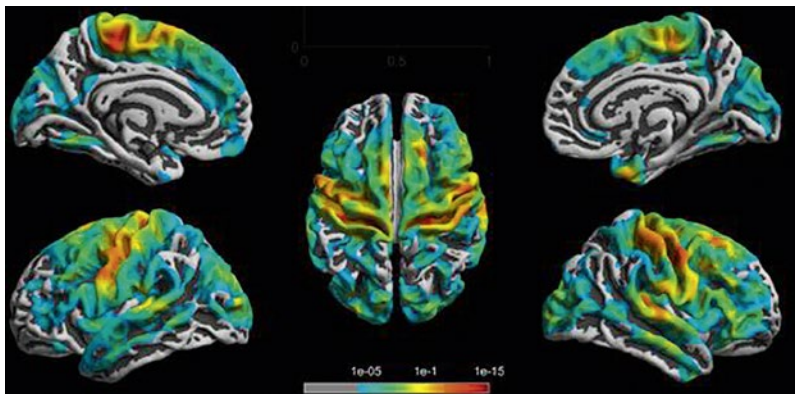
Precision medicine for cancer patients

MRI advances in Poland

MRI has developed rapidly over the past decade in Poland, where clinicians are combining MRI with PET and CT to highlight tumour growth or regression and perfusion. 'The fact that MRI offers new software and programmes means we can diagnose pathologies more precisely and make a diagnosis faster than a few years ago,' explained Poland's national advisor on radiology and diagnostic imaging Jerzy Walecki, during *Daniela Zimmermann's European Hospital* interview. 'What is so special about the value of modern MRI programmes,' he added, 'is that MRI offers structure and functional studies, and the combination and fusion of methods.'

MRI has undergone a rapid, dynamic and fascinating development over the last 10 years, which enables clinicians to diagnose faster and far more precisely. In addition, the fusion of a range of imaging techniques in MRI – so-called multiparametric MRI – is helping to deliver high levels of precision medicine and diagnostics for patients.

The buzzword in this area is parametric or multiparametric MRI. In prostate lesion studies for example, radiologists are using five different sequences to identify the invasiveness of a tumour and numerical scores such as PI-RADS one or two to predict the level of malignancy and growth. 'So, what we get nowadays is quantitative information about volume and dynamic of growth of the tumour as well as density, elasticity and stiffness of the tissue.'

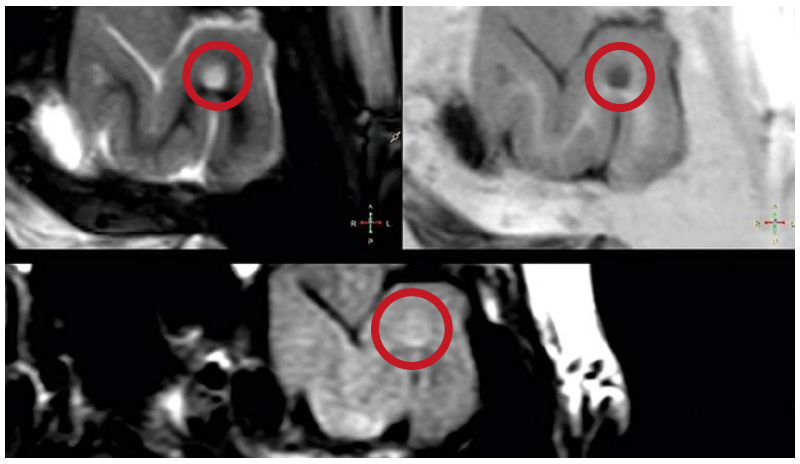


Images show regions of cortical atrophy in multiple sclerosis patients. Strongest regional cortical atrophy in precentral, postcentral, middle temporal, superior temporal and posterior cingulate gyri can be appreciated. Automated segmentation performed in Freesurfer. © Ewa Piatkowska-Janko, Michał Fraczek, Katarzyna Sklinda, Jerzy Walecki

In daily practice

In Walecki's department, where all types of diagnostic procedures are processed, he uses high and low Tesla systems and values the lower Tesla systems, such as the Aperto (0,4), open MRI systems from Hitachi, for the vertical field and open access. These provide clear benefits in anaesthetics cases and where access to patients for brain and trauma diagnostics is necessary, as well as in paediatrics, orthopaedics and for intervention procedures. 'As a primary diagnosis we also use the 0.4 Tesla system for Alzheimer's or tumour diagnoses, because the images are very clear and very good. Only when it comes to special features, such as functional MRI, spectroscopy or DTI and DWI, we switch in some cases to our 3 or 1.5 Tesla system,' Walecki explained.

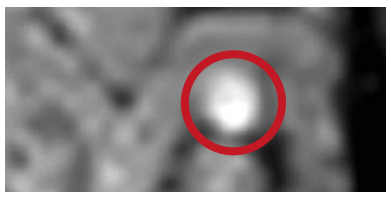
Parametric MRI enables a radiologist to classify a tumour in terms of volume, size, dynamic of growth, typical markers for malignancy and invasion of other organs, and to characterise the structural pattern of a lesion by obtaining information about the density and stiffness of the tissue. In addition, more techniques can be applied in oncology: spectroscopy, for example to differentiate between lesions and inflammation on a molecular level, whilst diffusion tensor imaging (DTI) is providing an important marker by showing the diffusion of water molecules.



Multiple sclerosis cortical lesions. Best assessed in IR and DIR. Highly specific for SM. Not present in migraine and NMO patients.

'The next option,' added Walecki, 'is functional MRI, especially before or after surgery, such as on brain tumours, where you gain information about the precise location of a tumour. This makes surgical planning possible by using functional MRI or mapping.'

Outlining how a combination of sequences and software with MRI delivers greater and quicker levels of precision, in terms of information about structures and tissue, he said: 'One software and one sequence of MRI is not enough for precise information about the character of a lesion.



© Michał Fraczek, Katarzyna Sklinda, Jerzy Walecki

By using many sequences and various softwares, you can obtain very precise information about the size and type of a tumour and its relationship to its neighbours.'

Combining MRI and PET as a hybrid method sees PET bringing added value in information about the metabolism of a lesion and recognition of activity in the lesion.

MRI conveys information about size, volume, and other features; PET delivers information about the activity of particular compounds to describe metabolic turnover of a lesion; and spectroscopy with MRI shows the presence and amounts of metabolites.

Finding new genes and proteins to explain disease

The mechanics of radiomics

Potentially, radiomics could generate new hypotheses and patient profiles, and probably discover new genes, a prominent French researcher explained in a dedicated New Horizons session at ECR 2018, reports Mélisande Rouger

Confirming or infirming hypotheses has long driven scientific research; however, this traditional and costly approach is giving way to data-driven initiatives, according to Professor Laure Fournier, a leading radiologist at Georges Pompidou European Hospital in Paris.

'Usually we formulate the hypothesis first and then take an image and analyse it. We like that in France; it comes from Descartes. The problem is that it's very expensive and time consuming, because each time you have an idea, you have to put together a research project,' she explained.

There has been a paradigm shift; researchers are now first looking at the data to try to extract meaning out of it before they formulate a hypothesis. 'This is discovery research,' Fournier observed. 'We're not validating something; we're trying to discover new things that we hadn't thought of.'

This is the same principle behind radiomics, which consists of extracting large sets of complex descriptors from clinical images, without any prior hypothesis.

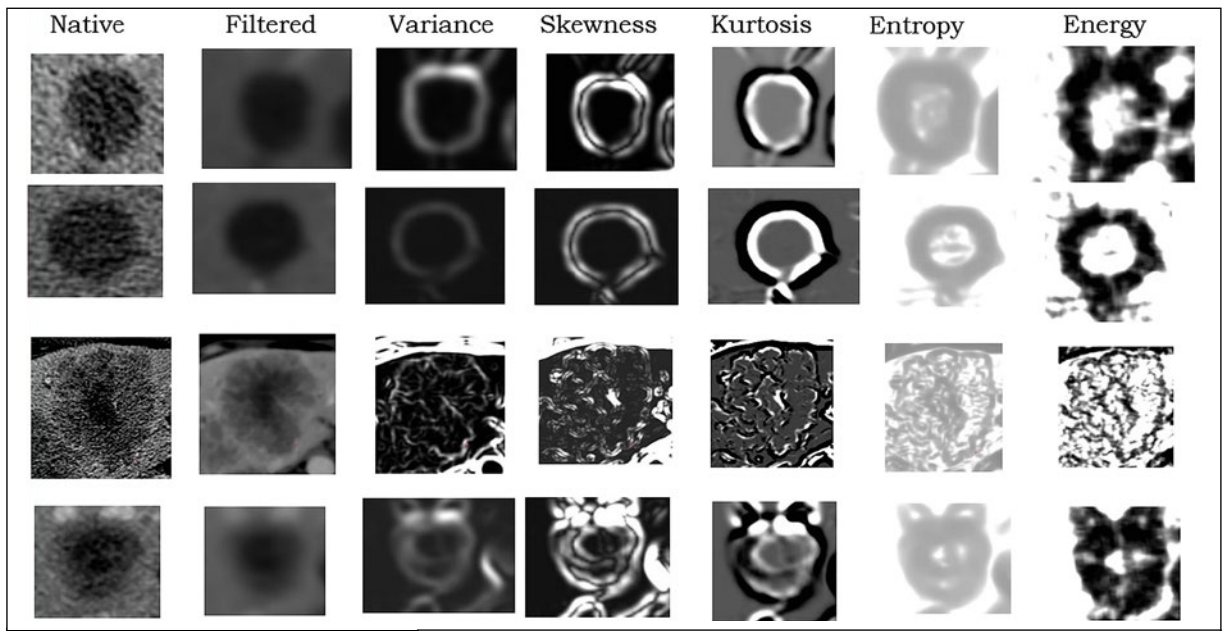
Images offer much more than just looking at size or morphology, Fournier emphasised. 'Images are phenotypes. What we want to stress and tell our clinicians is that an image is a reflection of all the biology that's going on underneath. There's a lot of information in our images besides measuring size in cancer, so we should try to get a lot more information from them.'

With radiomics, a wide variety of parameters – on tumour geometry, size, contours, anfractuosity, irregularity and directionality, as well as pixel composition – can be extracted from features from CT, MRI and PET studies. These data are then converted into high-dimensional data, and their mining is used to detect correlations with genomic patterns; this process is known as radiogenomics.

To use radiomics properly, one must first collect and extract all the data contained in an image. Then comes the process of data depuration, i.e. cleaning the data and making it uniform, and finally processing this data to select appropriate parameters.

'The most common way to process these parameters is by using a two-step approach: first we reduce the number of features based on their technical quality and then we test them for their clinical relevance,' Fournier explained.

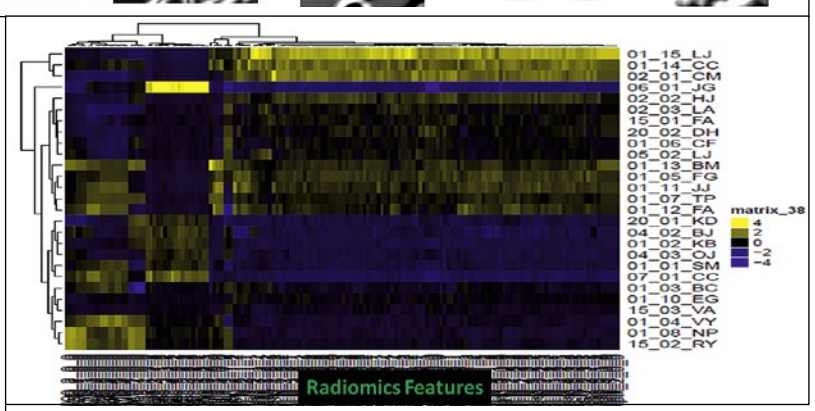
To process all the data in an image, dedicated software and AI tools are available in open source. Nonetheless, her team has developed its own software, which is now able to collect over 1,700 parameters per image, a capacity that tremendously improves the chance of not missing any relevant finding. 'These techniques are interesting to quantify heterogeneity on the pixel scale; they give more information than the human eye. They're more precise and subtle,' she said.



Texture analysis of liver metastases showing tumour heterogeneity. Processing of images allows generating a large number of parameters, which can be correlated to outcomes

Only a few parameters will be technically relevant. To reduce the number of features to those that truly matter, Fournier performs quality selection based on reproducibility. 'What we want is to select features that are reproducible. Another problem is that a lot of these parameters are very close to each other and may give you the same information. Once you get rid of useless parameters, you end up with a small number of features.'

As for clinical relevance, Fournier's team focused on identifying predictive radiomics signature to predict prognosis survival prediction – with good results. 'We obtained a PSS of almost three vs. 18 months, so this clearly separates two very different populations,' she said.



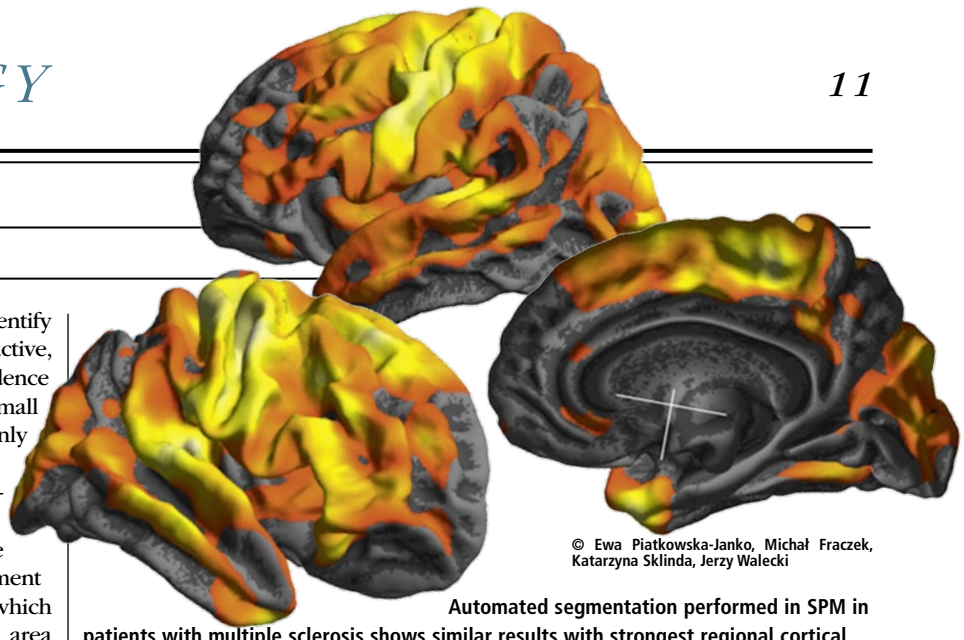
Heat map generated from 1700 parameters calculated from CT images of primitive renal carcinoma in a population of 27 patients. Imaging phenotypes emerge reflecting common expression patterns of imaging parameters in patients.

Jerzy Walecki, is professor of radiology, neuroradiology and radiodiagnostics and chairman of the radiology department at the Postgraduate Medical Centre in Warsaw, Poland. He is also National Consultant of Radiology for the Polish Health Ministry and heads the Medical Physics Committee of the Polish Academy of Science. In 1991, he launched the first Magnetic Resonance Laboratory in Poland. He is also the author of several books, monographs and over 200 scientific articles.

because, after treatment, a tumour may remain large or even enlarge but be empty inside. Here, a perfusion CT or MRI gives information about the level of perfusion, vascularisation and neoangiogenesis. 'A lack of flow inside means no neoangiogenesis, and means necrosis. Therefore, we must assess not only size but also tissue inside the tumour. Perfusion CT or MRI, spectroscopy and DTI are again the main methods to deliver precise results and therefore are so important in terms of precision medicine, and personalised medicine.'

The key question is to identify which part of a tumour is active, which part is 'sleeping', and evidence of necrosis. In cases of very small active parts of active tissue only PET can deliver results.

Professor Walecki's collaborators, intervention radiologists have used contrast MRI in the diagnosis and intravascular treatment of brain tumours to highlight which area has good flow and which area is necrotic. From there, targeted drug therapy is delivered to the tumour in a precision medicine approach.



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Automated segmentation performed in SPM in patients with multiple sclerosis shows similar results with strongest regional cortical atrophy in precentral, postcentral, middle temporal, superior temporal and posterior cingulate gyri. Cortical atrophy is an important hallmark of multiple sclerosis. Patterns of regional cortical atrophy can serve as a tool in diagnosis of early SM.

Approaching precision medicine

'In my opinion, MRI is the main tool for therapy control describing dynamic growth or regression of a lesion,' said Walecki, to explain the capability of MRI in oncology follow-up with a focus on personalised medicine and response to therapy. 'Parts of a tumour have completely different tissue densities and structures after treatment so, by using MRI and CT, we can observe differences in lesion density. 'Generally, MRI is more sensitive, more specific. Obviously, for shrinking or growing we can use CT as a good tool for evaluation of the size of a tumour.'

However, he stressed that tumour size is not always a relevant marker

Laure Fournier MD PhD is a radiologist at Georges Pompidou European Hospital in Paris, France, and Professor of Radiology at Paris Descartes University, Sorbonne Paris Cité.

Although software and AI tools are easy to use, radiologists need considerable help from bio-statisticians, engineers, data and computer scientists to operate radiomics properly. 'You will need a true multidisciplinary approach if you want to delve deep into radiomics,' Fournier pointed out.

One of the main challenges remains acquisition variability. 'We should work with data acquired from multicentre studies because, if parameters aren't reproducible in that setting, they're dumped in the garbage. So if we start with multicentre data, we can avoid that challenge,' she said. Integrating all the data, not just images, and having big cohorts are also paramount for the development of radiomics.

No doubt radiomics will significantly improve research, by allowing testing simultaneously a very large number of new parameters that are extracted from images, Fournier believes. 'The idea is that new biomarkers will emerge, and to pan all these biomarkers and generate new hypotheses. Radiomics might lead us to new patient profiles and find new genes and proteins that might explain disease.'

The impact of a radiological transformation

MR Fingerprinting and Compressed Sensing

MR Fingerprinting and Compressed Sensing are two procedures that will facilitate much faster MR sequencing than currently possible – and more. 'MR Fingerprinting will revolutionise MRI scanning,' according to Dr Siegfried Trattnig, head of the Centre of Excellence for High-Field MRI at the Medical University of Vienna in Austria. 'It will completely change the way MRI scans are currently being carried out.'

Report: Michael Krassnitzer

MR Fingerprinting will make it possible to produce very individual quantitative maps of a patient's tissue, so-called T1 and T2 maps (the longitudinal relaxation time T1 and the transverse relaxation time T2, together with the proton density, are the basic parameters of MRI). They virtually create an MRI fingerprint of a patient, as Trattnig explains: 'The maps created with MRF are not dependent on the sequence or the scanner. No matter whether a patient is examined in Vienna, Heidelberg, or New York: MRF always delivers the same results. This is therefore the first ever chance to standardise MRI and to use it advantageously in multicentre studies.'

One stop shopping

MRF also opens up other opportunities: 'T1 and T2 maps can be used to produce the conventional contrast images that radiologists are familiar with, arbitrarily,' Trattnig confirms. This speeds up processes significantly. Trattnig refers to it as 'one stop shopping'. 'An individual sequence, which lasts about five minutes, produces all quantitative data – T1, T2, proton density – and additionally we are able to produce all the contrast images from this data hitherto produced with the previous conventional imaging procedure.'

The principle behind this is not that easy to explain. 'MRF is a fundamentally new approach for carrying out MRI scans,' Trattnig explains. So far, MR images were built on the T1 or T2 relaxation curves with fixed sequence parameters (such as TR time or flip angle). However, MRF has no fixed parameters. 'A single spiral sequence acquires a large number of images, with the parameters for each individual one of these images varying at random,' the radiologist explains.

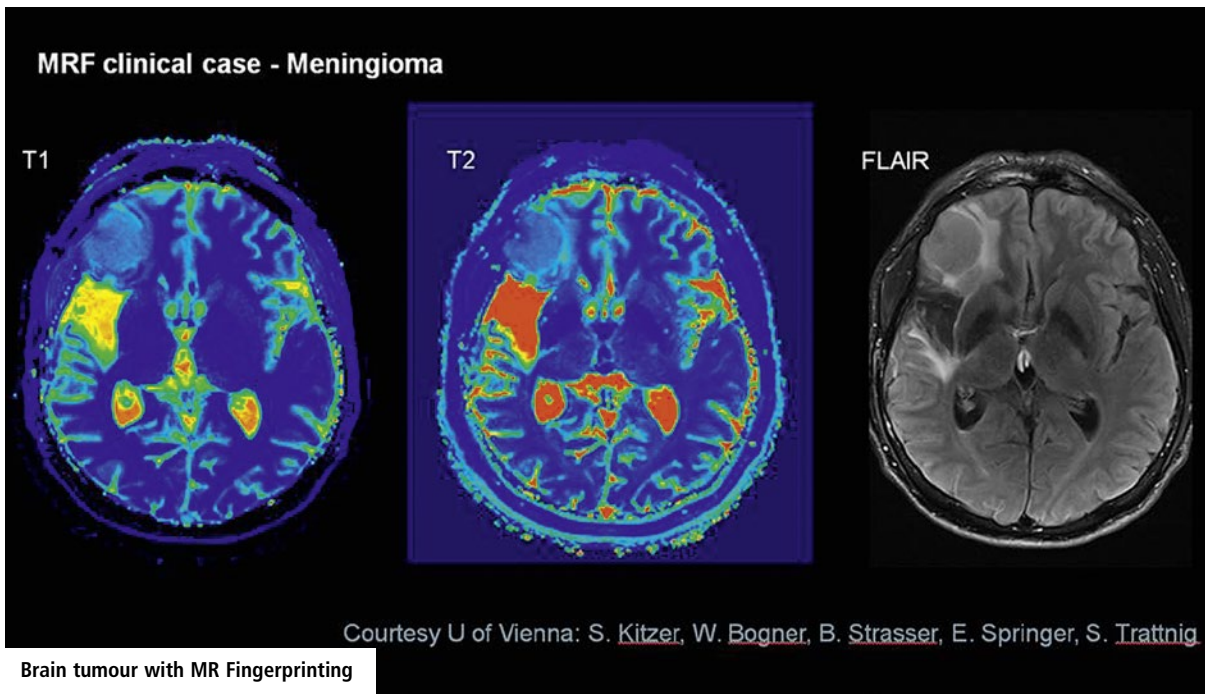
Within 30 to 40 seconds, 3,000 to 5,000 images with different TR times and flip angles are being created. On their own, these images are of low quality as only individual points of a k-space are reconstructed.

However, if one of these points (pixels) is tracked on all images, one obtains a meaningful signal intensity curve over time for this pixel.

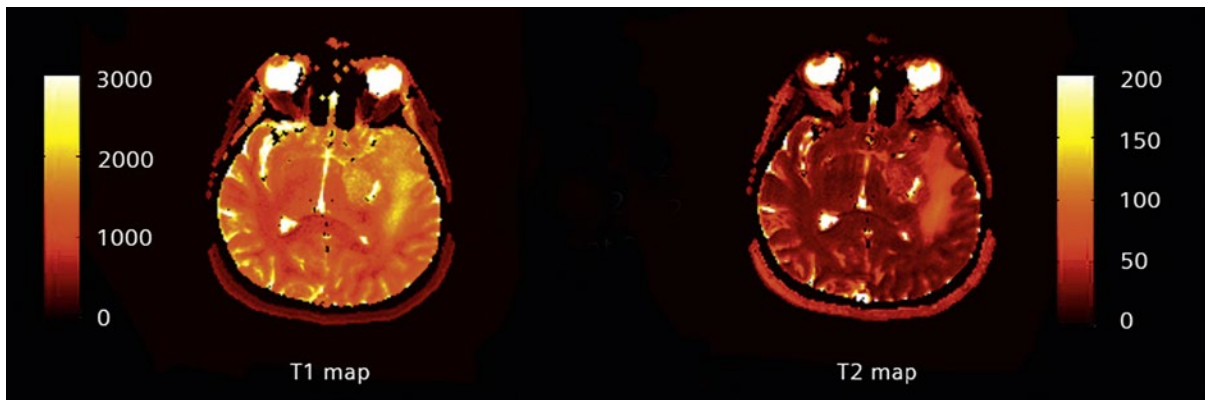
This signal intensity curve represents the MRI 'fingerprint' for the patient. It is then compared with a database (dictionary). This database can calculate the Bloch equations using the randomly selected sequence parameters and the expected T1 and T2 relaxation times of the tissue examined.

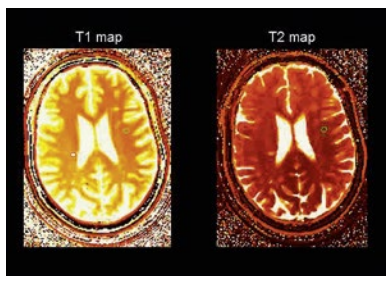
Using a pattern recognition tool, the best match of the patient's MR Fingerprint (the individual signal intensity curve) with the database is established and this best match shows the patient's precise T1 and T2 distribution, as well as proton density distribution within the tissue based on T1 and T2 maps.

Cardiac imaging is one of the possible clinical applications. T1 mapping is becoming increasingly important for dilated or hypertrophic cardiomyopathy or myocarditis. 'T1 mapping without MRF however is time-consuming, with a sequence taking up to 8 – 10 minutes,' explains Trattnig: 'With MRF, we can create T1 and T2 maps with a single breath hold and then produce contrast images synthetically using the data.'



Brain tumour with MR Fingerprinting





MRF: Asymptomatic patient with multiple sclerosis Images courtesy of Prof. Trattnig, Medical University of Vienna, Austria

MRF has the potential to provide quantitative parameters, to help differentiate tumours in the brain
Images courtesy of Prof. Trattnig, Medical University of Vienna, Austria

An MRI scan usually takes so long because a large number of points is read from the MRI raw data matrix (k-space) to produce images. 'Many points in the kspace are actually irrelevant for the specific examination,' Trattnig explains. The best example for compressed sensing is MRI angiography, for which only the blood vessels are relevant but not the surrounding tissue. According to an overview study, compressed sensing can speed up MRI angiography by factor 12.5.

Source: MedUni Vienna/Hammerschmidt

Dr Siegfried Trattnig is a Professor for Radiology focusing on High-Field MRI at the Medical University of Vienna in Austria, where he has also been medical director of the High-Field MRI Research Scanner since 2000 and medical director of the High Field MRI Centre (HFMRC) since its foundation in 2003. The professor is also a member of more than 50 committees in all important international radiological, orthopaedic and MRI associations and has authored more than 480 specialist articles.

Areas of application

Whilst MR Fingerprinting is still at an experimental stage, compressed sensing is already being trialled in clinical routine. A new 3-Tesla scanner from Siemens is already offering compressed sensing for examinations of the abdomen and liver. 'The patient can breathe normally whilst kspace data is continuously being acquired and then retrospectively reconstructed,' Trattnig explains.

It can also be used favourably in cardiac imaging for patients with arrhythmia or limited lung function. Previously, radiologists had to choose between high temporal or high spatial resolution: 'For the first time ever, with compressed sensing, both is possible simultaneously,' Trattnig points out. This facilitates better detection of tumours and improved differential diagnosis.

Trattnig believes that compressed sensing can also be used in paediatric radiology. At the moment, carrying out MRI scans for small children involves sedation or an anaesthetic; this can later have a negative impact on neurocognitive abilities during development. With the fast sequences made possible through compressed sensing, an MRI angiography, for instance, can be carried out much faster for small children, helping to reduce the time required for sedation or general anaesthetic considerably.

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1. Data on file and from public sources, 2017. **2.** Results from Friedewald, SM, et al. "Breast cancer screening using tomosynthesis in combination with digital mammography." JAMA 311.24 (2014): 2499-2507; a multi-site (13), non-randomized, historical control study of 454,000 screening mammograms investigating the initial impact of the introduction of the Hologic Selenia® Dimensions® on screening outcomes. Individual results may vary. The study found an average 41% increase and that 1.2 (95% CI: 0.8-1.6) additional invasive breast cancers per 1000 screening exams were found in women receiving combined 2D FFDM and 3D™ mammograms acquired with the Hologic 3D™ Mammography System versus women receiving 2D FFDM mammograms only. **3.** In an internal study comparing Hologic's standard compression technology to the SmartCurve™ system (18 x 24cm).

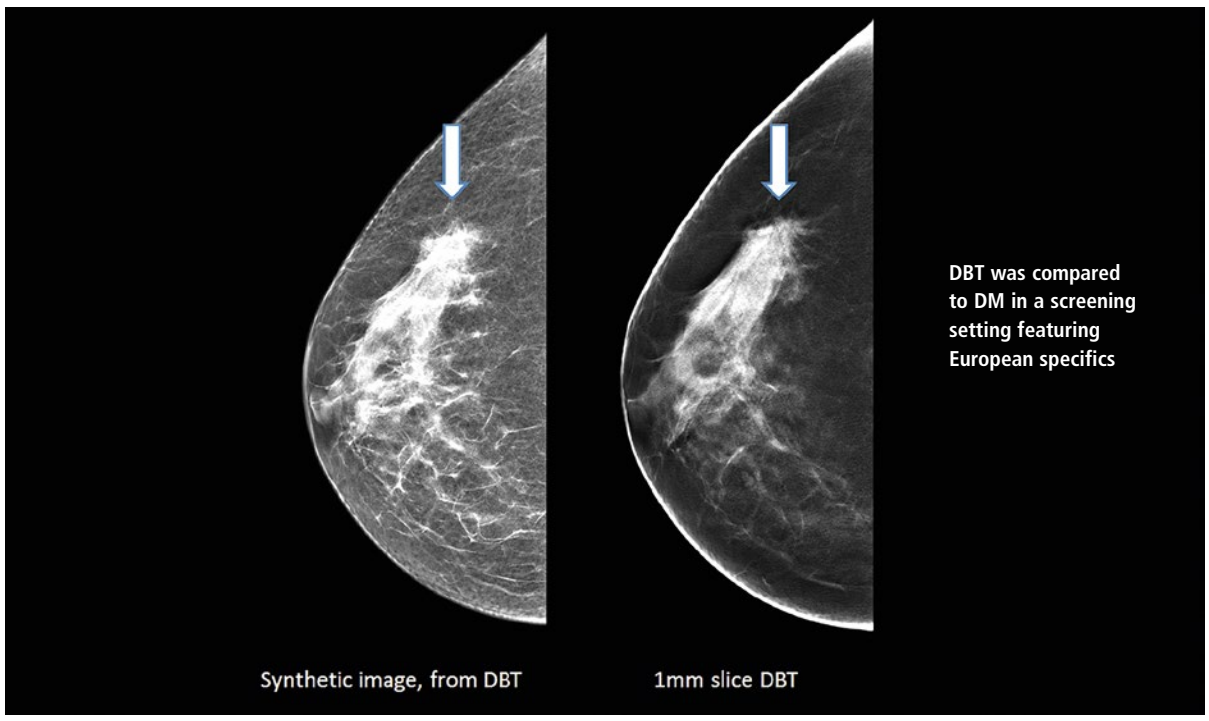
Norwegian trial studies tomosynthesis benefits

To-Be for TOMO

The UNESCO World Heritage City Bergen is seen as the gateway to the fiords of Norway. However, for radiologists the city offers an even more interesting attraction than Scandinavian landscapes. Bergen features one of the largest randomised control trials to compare digital breast tomosynthesis (DBT) with digital mammography (DM): the To-Be trial. Professor Solveig Hofvind, head of BreastScreen Norway, outlined the study and its promising interim results at ECR 2018.

Report: Lena Petzold

'There were several reasons why we wanted to start this specific trial,' Professor Solveig Hofvind says, to explain the value of the To-Be trial. 'A number of studies have already shown a higher cancer detection rate for tomosynthesis compared to digital mammography. However, most of these used DM in addition to DBT, which meant doubling the radiation dose for women. Furthermore, many studies were performed in the USA in a much broader range. 'We wanted to compare DBT and synthetic 2-D mammograms against digital mammography in a screening setting featuring European specifics and matching the gold standard criteria,' she says, and underlines that the European perspective is especially important when it comes to recall rates. 'The USA recall rate is between ten and fifteen per cent, whilst in Europe it is between three and five percent. Although the rate reduction through tomosynthesis is a great achievement for women in the States, it is a much more difficult task to achieve in Europe and should therefore be studied separately.'



DBT was compared to DM in a screening setting featuring European specifics

A great advantage of the trial is that the study group has access to important follow-up clinical data of more than 99.9 per cent of their participating patients. All women diagnosed with breast cancer in Norway are included in the Norwegian cancer registry, so the group can access this data for their participants and closely follow their progress.

To-Be 1

The To-Be trial consists of two parts. In To-Be 1, DBT and synthetic 2-D mammograms are tested against digital mammography in a screening setting using equipment from GE Healthcare.

All women in Norway age 50 to 69 are offered a mammography screening every two years. The attendance rate per screening round is 75 percent, so the coverage is very high, Hofvind confirms. Norway has 30 screening units, but only one in Bergen. For To-Be 1, all women who attended the breast screening unit in Bergen in 2016 and 2017 were asked about participation. Those who said 'yes' signed an informed consent and were electronically randomised into digital mammography or tomosynthesis afterwards. The participation rate was close to 90 percent; so about 30,000 women were screened. 'In Norway we do independent double reading with consensus or arbitration, as in most European countries,' the expert adds.

The aim of To-Be 1 is to compare the early screening outcome and economic cost of screening with DBT vs. DM in a population-based screening program. The interim analysis focuses on interpretation time, consensus and recall rate as well as on the stratification of data by mammographic density measured via an automated system. 'We also want to look at the rate of interval cancers detected between two screening rounds. Therefore we have to wait two years after the last woman was screened for the data to become available.'

To specifically determine the cost of DBT vs. DM, the study team coded every process step, from time spent on consensus to diagnostics, as well as treatment per screen-detected cancer.

The radiographers and radiologists who worked with To-Be 1

New Italian study results

Pre-operative MRI endorsed for breast cancer

MRI offers unequalled sensitivity and specificity in breast cancer detection. Yet, it is poorly accepted pre-operatively. Recently, eminent radiologist Francesco Sardanelli, professor for radiology at Milan University and Chief of Radiology at the IRCCS Policlinico San Donato in Italy, unveiled preliminary results that could further MRI acceptance among multidisciplinary teams.

Report: Mélisande Rouger

Although the new American Society of Breast Surgeons guidelines recommend not using routine MRI in new cancer patients, it is crucial for radiologists to understand surgeons' needs and know in which cases MRI can bring value over other modalities to help detect breast cancer (BC), according to Sardanelli, He has reviewed the topic extensively and notably took part in a study comparing sensitivity of MRI vs. mammography to detect multifocal multicentric BC (Sardanelli et al, AJR 2004), dubbed the 'absolute sensitivity' study.

Sardanelli and co-researchers identified all false negatives and false positives of MRI using mastectomy with a 5-mm pathological examination of the whole breast as a standard reference. 'Based on the analysis of 188 cancer lesions, sensitivity of MRI was significantly higher (81%) than that of double reading mammography (66%) while positive predictive value was not significantly different (about 70%). Many other studies confirmed the high diagnostic performance of breast MRI in the preoperative setting,' he said.

MRI is usually the second or third imaging test after a suspect is spotted on a mammogram or ultrasound, to visualise T-extension and identify satellite or contralateral lesions. A more recent multicentric international study demonstrated that preoperative MRI clinically offers, sensitivity as high as 95% and specificity between 90 and 97% (Sardanelli et al, Invest Radiol 2016).

Marking disease extent

MRI's strength is to detect cancers that are biologically relevant. In a study at Memorial Sloane Kettering Center in NYC (Iacconi et al, Radiology 2016), 76% of cancers picked up by MRI were invasive, 25% were larger than 1-cm, 23% larger than the known cancer index, and 5% biologically more important. 'This data matters because we are more and more aware as radiologists that our task is not to detect all the cancers but really those that are biologically meaningful,' Sardanelli explained.

'MRI can give a clear idea of what the disease extension. The diagnostic performance is not under discussion, but rather why not accept a test with such a high performance in preoperative setting?' Sardanelli questioned.

Surgeons may have had good reasons for not accepting a highly sensitive and specific test in the preoperative setting, he explained. 'It was demonstrated long ago that even if you have conservative treatment and whole breast radiotherapy, you don't have a difference in survival in comparison to mastectomy. So, there is a possible rationale for suspecting that, with MRI, you could have unnecessary mastectomies, i.e. over diagnosis and over-treatment.'

A second point, he added, is the non-negligible risk of positive margins and re-operation when a strictly conservative treatment is performed, reported to be as high as 20% or more. Here MRI could give information enabling surgeons to be more precise in tissue removal, reducing the re-operation rate.

About eight years ago, Sardanelli established indications for breast MRI within the European Society of Breast Cancer Specialists (EUSOMA) (Sardanelli et al, Eur J Cancer 2010). A multidisciplinary group concurred on using preoperative MRI for these indications: newly diagnosed cancer and high-risk women; mammography/US discrepancy of more than 1-cm in women over 60; and for eligibility to partial breast irradiation (PBI).

This last indication has been confirmed by a meta-analysis (Di Leo et al, Radiology 2015) showing that MRI contradicted verdict in 11% of the cases a patient was deemed eligible for PBI based on conventional imaging.

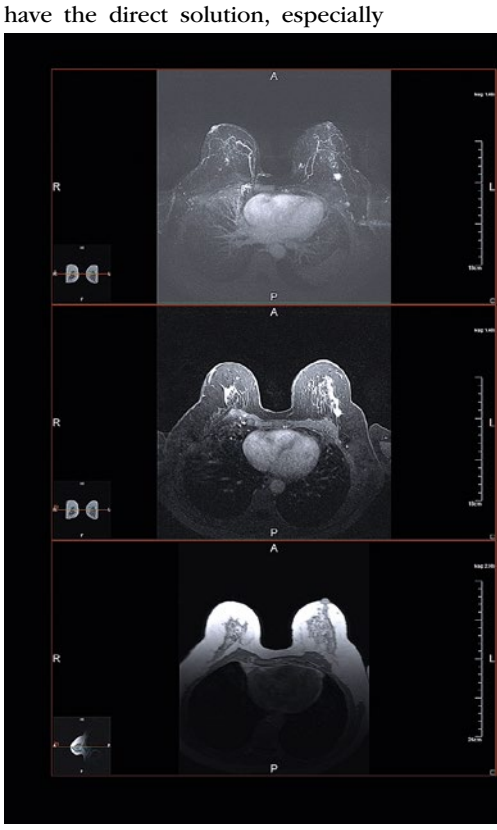
'It's a pity that MRI is not largely used for this purpose. Thus, we offer PBI to several women that should undergo whole breast irradiation and probably also negate PBI to other women who could benefit from reducing radiation' Sardanelli pointed out.

Exploiting the negative predictive value

'These EUSOMA indications still hold, Sardanelli added, but he has since received new feedback. 'Surgeons told me that MRI is often already performed for diagnostic purposes and that they had to work with this information anyway. So you cannot cancel MRI when it was used to detect cancer in high-risk women, and you must use that data also when MRI detects cancer for problem solving, including pathological nipple discharge, after NAC, or to detect otherwise occult primary BC,' he said.

'High-risk (so-called B3) lesions at imaging-guided needle biopsy could also be another important indication for MRI. 'Exploiting its high negative predictive value, we can use MRI to do less surgery, not more.'

To apply evidence-based rules to preoperative MRI is tough and more studies are needed. 'We don't have the direct solution, especially



have been blinded for study specific results during the study period. Only usual quality assurance has been performed and reported according to the guidelines.

To-Be 2

The second part of the trial, To-Be 2, is a follow-up of the first analysis. All women who will attend the screening program in Bergen in 2018 and 2019 will be asked about participation and those agreeing will be screened with DBT and synthetic digital mammography. During the first 6 months, 93% agreed to participate. A certain number of the contributing women will have already participated in To-Be 1. 'This means we can see the implications of using tomosynthesis after tomosynthesis, which will provide vital information. If we are to implement DBT in a screening program, we will use it every two years.

'It is important to know if, for example, the increased detection rate still applies if we screen with tomosynthesis a second, third or sixth time,' she explains. Within the first few months, the participation rate has already been over 93 percent. Just like To-Be 1, the second part of the trial will focus on performance, detection rate, as well as economical costs and consider interval cancers. Therefore the data will be ready for use in 2021.

'We are expecting very interesting and relevant results from both parts of the trial,' Hofvind believes. However, if the conclusions will further the process of including tomosynthesis in the Norwegian screening program remains to be seen. 'We need more evidence to decide whether the technology really provides improvements.

'There are growing concerns about over-diagnosis and we should not take these lightly. If tomosynthesis is mostly detecting the small and slow-growing dormant tumours, we need to know and evaluate this fact, because after all,' Hofvind emphasises. 'Our goal in screening is to detect the killing cancers in time.

Professor Solveig Hofvind PhD heads the Norwegian breast cancer screening program, BreastScreen Norway, and is also a radiography lecturer at Oslo Metropolitan University. Having trained as a radiographer, she also obtained a master's degree at the Norwegian school of sport sciences. Hofvind pioneered a breast clinic and the Norwegian breast cancer screening program at Akershus University hospital in Lørenskog, Norway, before she began to work for Norway's cancer registry in 1998. Her PhD, granted in 2005, was gained for her thesis focused on the Norwegian breast cancer screening program.

Heard at the EBCC11 in Barcelona

Identifying circulating cancer cells

Liquid biopsies can increasingly help diagnose and monitor breast cancer, and tracking circulating tumour cells (CTC) in metastatic patients could prove effective in these applications and treatment planning. Efforts are currently underway to demonstrate CTC clinical use and much can be learned from completed studies in prostate cancer, speaker Michail Ignatiadis MD PhD highlighted in a dedicated session at EBCC11 held this March in Spain.

Identifying and characterising circulating tumour cells (CTC) in cancer patients provides unique insights into metastatic disease, which is responsible for over 90% of cancer deaths. CTC detection could also help unravel new therapeutic targets for cancer treatment.

However, the clinical use of CTC identification in breast cancer remains to be established, according to Michail Ignatiadis, oncologist at Jules Bordet Institute ULB. 'No convincing evidence for the clinical use of CTCs has been demonstrated in breast cancer so far. But what we know is that CTCs in metastatic BC are associated with worst outcome,' he said.

A large meta analysis, including the data of almost 2,000 patients from different countries, showed that detecting 5 CTC was associated with significantly worst progression free survival (PFS). 'If the patient had at least 5 CTS, the median PFS was 6.5 months and it was double if the patient had no CTC. Similarly for overall survival, researchers observed a large separation of the curve, and patients with 5 CTCs had 15 months of survival vs. 37 months for patients with no CTCs. Having at least 5 CTCs is a very bad prognostic marker,' Ignatiadis explained.

The main, and so far only, reported study assessing the value of CTC in treatment monitoring – the SWOG S0500 trial – has not showed any improvement in PFS or overall survival compared to waiting for progression to be confirmed by imaging. However investigators of the study did not use a targeted approach and did not have a good alternative treatment for these patients who were progressing early on chemotherapy, Ignatiadis pointed out. 'They offered another chemo, so it was not a tailored treatment and this is the main reason for the study failure. CTC were used simply as a prognostic, not as a predictive indicator as to whether treatment could work or not.'

Much more relevant information does exist in prostate cancer (PC), including a meta analysis of five different studies enrolling over 6,000 patients with castration resistant PC, to determine whether CTC response and prostate-specific antigen (PSA) could predict overall survival after 13 weeks of treatment. Researchers compared CTC and PSA conversion rates, and observed that CTC enabled distinction between patients with good and bad prognosis in terms of overall survival with the highest discriminating power. The CTC marker was better than the PSA conversion currently used by many clinical oncologists.

Ignatiadis: 'These results show that CTC in prostate cancer could be used for early readout of drug activity, when one is testing new compounds. After 13 weeks of treatment, one can already know if a new drug is working or not. If this is endorsed by the FDA, it could be implemented as an early biomarker of response to check for drug activity and prioritise drug development.'

For non-metastatic breast cancer, clinical validity of CTCs in early disease has been established. In a study published in JNCI, Bidard and co. showed that CTC detection before neoadjuvant therapy begins is associated with shorter distant disease-free survival. 'The data, collected in over 1,500 patients, shows that if you have no CTC to start with, you have a very good prognosis. But if you have 5 CTCs you have a very bad prognosis. And as the number of CTC increases, prognosis becomes worse,' he said.

Although CTCs are included in the cM0(i+) micrometastatic disease classification of AJCC staging, their clinical utility in early BC remains to be proven. One effort was made by Ignatiadis and co. in the EORTC-led Treat CTC Trial. In this, women with HER2-negative non-metastatic breast cancer and detectable CTC following (neo) adjuvant chemotherapy and surgery were randomised between 18 weeks of trastuzumab vs. observation.

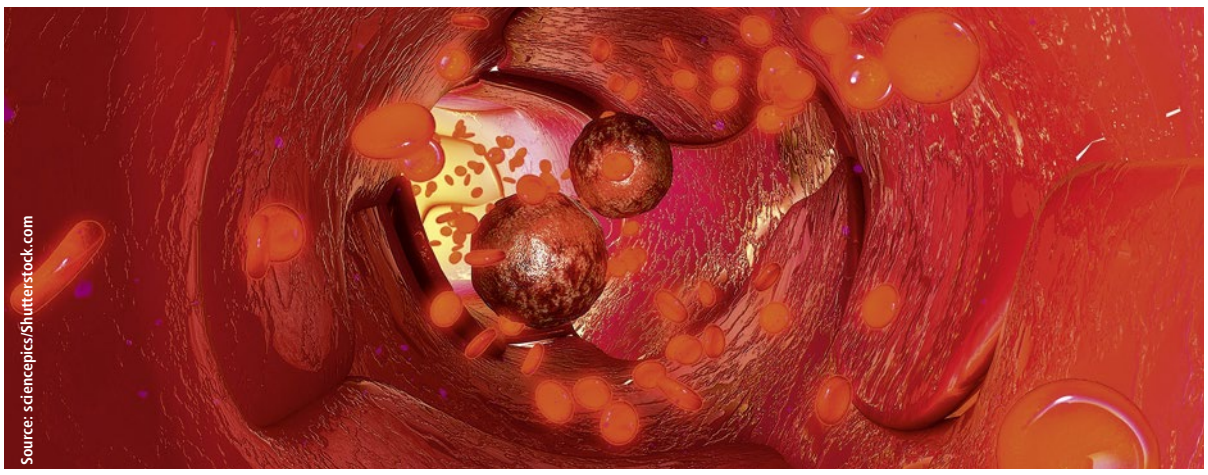
The trial's primary aim was to demonstrate that trastuzumab could eliminate CTCs at week 18 as an early signal of drug activity in this setting. The Treat CTC trial randomised 63 patients and demonstrated that trastuzumab could not eliminate CTCs. This trial's results lined up with those reported at the 2017 San Antonio Breast Cancer Symposium, i.e. the NSABP-B47 phase 3 trial, which randomised around 3,000 women with HER2-low breast cancer between one year of trastuzumab vs. observation. The NSABP-B47 trial showed no difference in the five-year invasive, disease-free survival between both groups.

'We need more examples, such as the Treat CTC and NSABP-B47 trials using different drugs, to confirm the hypothesis that CTC or circulating tumour DNA (ctDNA) clearance after two or three months of treatment can be an early signal of drug activity. If further such evidence is provided, one could use this information in addition to data on drug activity in the metastatic and neoadjuvant settings, to better inform decisions about whether or not to move forward a new drug in testing in the adjuvant setting. This could eventually lead to a new model for drug development,' Ignatiadis said.

In the future, oncologists could also use molecular analysis of CTC or ctDNA, to help provide functional information on drug sensitivity. Characterising CTC at the RNA, DNA or protein levels, or by injecting CTC in mice, one can gain evidence of drug activity in a preclinical model, according to Ignatiadis. 'However, it's still early days and there is no clinical effort to test such approaches in clinical trials yet.'

For the moment, early CTC response at week 13 is a robust response biomarker associated with improved overall survival in metastatic castration resistant PC, and CTC at week 13 might be used to accelerate drug development in this setting. However, he concluded, more studies are needed to provide evidence that early CTC or ctDNA response can be used as an early response biomarker in non-metastatic BC to accelerate drug development.

Michail Ignatiadis MD PhD is attending physician at the Medical Oncology Department, Jules Bordet Institute and assistant professor at the Université Libre de Bruxelles, Brussels, Belgium. He also leads the Academic Trials Promoting Team at the Jules Bordet Institute, where he works on stimulating and streamlining the development of investigator-initiated trials across all tumour types and disciplines. Another responsibility is fundraising and discussions with the pharmaceutical industry. He is particularly interested in drug and biomarker development for breast cancer. His work in the field of blood-based biomarkers is internationally recognised.



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Tracking circulating tumour cells could help unravel new therapeutic targets for breast cancer treatment

when we consider the different aims: estimation of T-extent, detection of ipsilateral cancerous lesions; screening of synchronous contralateral cancers.'

Several studies show that researchers usually know what happens in terms of therapy after MRI, but not what the therapy plan was before using the modality. Preliminary results of the MIPA study, which compares patients who received preoperative MRI with patients who didn't in about 30 highly qualified centres, are now available for about 2,500 patients.

Data show that: 1) preoperative MRI was performed in about 50% of women after BC diagnosis; 2) about 17% had cancer diagnosed with MRI, so no decision was taken; 3) in 40% of the cases, surgeons were involved in requesting MRI; 4) MRI triggers only about 1-2% of additional mastectomies; 'MRI does not prompt mastectomy but, paradoxically, mastectomy prompts MRI.

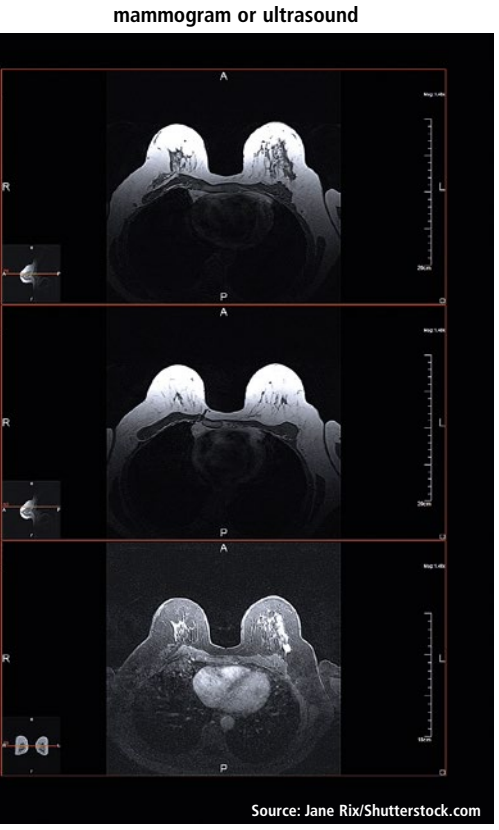
'So MRI is rightly used by surgeons as a confirmation tool for mastectomy,' Sardanelli said.

Enabling tailored conservative treatment

Additionally, after MRI, about 13-14% of patients had less extensive conservative surgery if compared to that planned before MRI; a similar percentage had a more extensive conservative surgery. 'This means that MRI tailored the conservative treatment and allowed personalised surgery', he added. 'These results only show that, in highly specialised centres, radiologists and surgeons can communicate and that surgeons learned the best use of preoperative MRI.'

Francesco Sardanelli, professor of radiology at Milan University and director of the radiology unit at San Donato Hospital in Milan, Italy, also directs the European Network for Assessment of Imaging in Medicine and is editor-in-chief of European Radiology Experimental.

MRI is usually the second or third imaging test after a suspect is spotted on a mammogram or ultrasound



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