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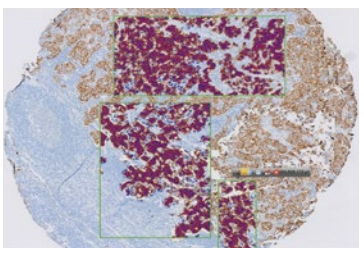
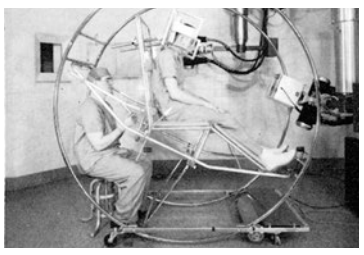


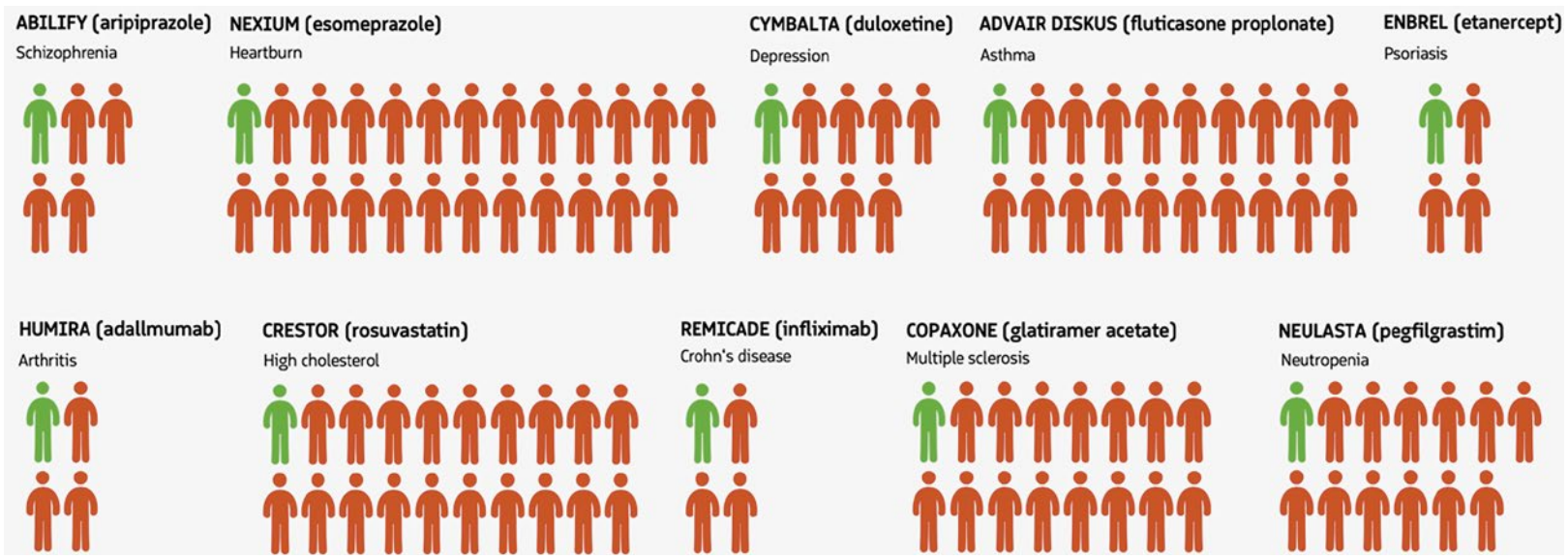


RADIOLOGY

- **Artificial intelligence: the time has come**
- **Man and machine: today's centaur**
- **Radiomics on tap in 5-10 years**

The end of medicine as we know it

The physician is no longer the lone master of diagnosis



Inefficiency of current pharmaceutical treatments: the green patients represent those for whom a medicine works; although the reds are prescribed that same medication it delivers no benefit adapted from Scannell et al. (2012) Nat Rev Drug Discov 11(3):191-200

Currently many researchers and experts assume that the next great socio-economic revolution will include a completely new definition of health and how we define illnesses and therapies. According to Professor Harald Schmidt, head of the Department of Pharmacology and Personalised Medicine, Faculty for Health, Medicine and Life Sciences at the University of Maastricht, 'Our health system today can no longer be sustained in its existing form. It has become too expensive and too ineffective.'

The end of medicine, as we know it? Asked for a fuller explanation of his prediction, he pointed to a fundamental problem. 'Our definition of illness is based on organ localisation or individual symptoms. All medicine, as we teach it, in the way we train specialists, the way our clinics are structured, is divided according to organs. There is a specialist physician and clinic for every organ.

'However, illnesses do not function that way, rather we experience disruptions in the signal systems in our cells – put more precisely, in certain hotspots that are disturbed and cause symptoms. In most cases these signal disruptions occur in more than one organ and produce different symptoms. Thanks to the organ-based division, we do not see that though. And thus there are hardly any systematic or holistic approaches to medicine.

'The pharmaceutical industry is also contributing to the end of medicine as we know it, doomed in its current form. In the list of the world's ten largest companies there is not a single pharmaceutical company any more. That is somehow logical because why should we be forever discovering new medicines?

'One reason why, after 100 years of pharmaceutical industry, we are still researching for new medicines is the lack of precise illness definitions and the chronic treatment of symptoms instead of healing. To date we know the molecular causes of very few illnesses and therefore cannot treat them.'

Medical education must change

'Medical education will have to change along with hospital structures. Physicians will have to work in interdisciplinary teams more often, together with bioinformatics specialists and system physicians. Actually the days when the medical specialist treats a patient based on his personal current knowledge are now already over.

'A research phase will precede these changes. But, it's clear to see that such a medicine will lead to significantly more interdisciplinary hospital structures. Thus, the first clinics have already introduced immune disease boards. In these boards, illnesses such as psoriasis, asthma, colitis or rheumatoid arthritis are treated by a team, working like the familiar tumour boards for oncological issues. Even experts agree that these disease designations are obsolete. These are essentially immune system diseases that have to be defined molecularly and not by clinical morphological means.

'We also have to bid farewell to classical pathology, currently exhausted by histology and the detailed description of cell changes. More than anything we need a molecular pathology that leads to molecular disease definitions and thus permits precise diagnosis and therapy. To attain this, we have to work more in terms of systems and more holistically.

'Once we have penetrated deeply enough to identify the disease mechanisms, then we can apply a precisely suited medication – possibly one that has already been approved.

'In the not too distant future there will be at least one appropriate medication for all the disease mechanisms so defined, the number of which will be between 160 and 200. Thus a research and development pharmaceutical industry is obsolete; only manufacturers and distributors will still be needed. Only those pharmaceutical enterprises that heal rather than treat will survive.

'The first steps have been taken in this direction. In 2018, the USA's FDA approved tumour medications that are no longer approved to treat an organ tumour – but for an oncological mechanism, which means they are approved for the specific mechanism, regardless of where the tumour is found. That is a small turning point for medication therapy.'

The AI or big data impact on health systems

'Despite necessary changes, initially, the treatment cycle will naturally stay the same: as a rule the patient with organ-based symptoms will look for a physician, only his diagnosis will be strongly supported by artificial intelligence. Perhaps AI will propose to the physician additional measurement parameters, digital imaging or genetic examinations and thus determine a molecular illness diagnosis. Then just like today it will be the task of the medical team to support the patient in choosing the optimum therapy for him.

'The physician is no longer the lone master of diagnosis – he cannot be that any more. The networked data analysis necessary to analyse big data will be possible everywhere. Nonetheless there will still be precise ad hoc diagnoses and manual therapies, such as the surgical specialties. However, there will be big changes in the field of chronic illnesses.'

AI will not make a therapy decision

'Currently the most common cause of death is physician's error – we already have the problem. The computer does not administer therapy; AI proposes a diagnosis with a probability of x and the therapy appropriate to it. The decision as to which way to go is reserved for the medical team, the patients and their priorities.'

Physician, chemist and pharmacist **Professor Harald Schmidt** chairs the Department of Pharmacology and Personalised Medicine, at the Faculty for Health, Medicine and Life Sciences, University of Maastricht. As advanced investigator of the European Research Council (ERC) he also leads various research programmes, among them a Proof-of-Concept study on strokes; the COST Action OpenMultiMed on system medicine and the Horizon 2020 programme REPO-TRIAL. Schmidt was co-founder and managing director of Vasopharm GmbH, is co-publisher of the journal Systems Medicine and has written more than 200 refereed international publications, summary articles and books.

Announcement:
Professor Harald Schmidt (Maastricht) will discuss 'The end of medicine as we know it' at the ETIM 2019 - Artificial Intelligence and Smart Hospital Summit
Saturday 23 February 2019.
Time: 3:55-4:30 pm

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French government keen to introduce AI into healthcare

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The concept of artificial intelligence (AI) has been touted as an important aid for healthcare for at least a decade. However, despite years of research and major technical and scientific advances we are only at the beginning of its use in a medical environment. For artificial intelligence to function correctly huge amounts of relevant data need to be accessible to its algorithms.

France is conscious of being behind other European countries, namely the UK, Netherlands and Denmark, the USA and Canada, in terms of cross-referencing the data sources required. This is particularly surprising as the French have a unique resource of centralised public databases, medical, social and financial, managed by governmental organisations but until now kept separately. This will change during 2019 when, thanks to a government initiative "AI for humanity", grants will be awarded to public-private consortia capable of putting in place the mechanisms for cross-referencing and managing these data in a way that is fully exploitable within three years. Actors are invited from all sectors (health, transport, agriculture etc.) with the aim of joining expertise and experience in order to be as efficient as possible. Obviously, this has to be within European norms for the protection of personal information.

As the very thought of AI is often frightening to the general public, President Macron has pledged to be completely transparent about the algorithms being used and educational programmes based on the advances made will be put in place so people are aware of the changes coming.

In the health sector where surgical robots and AI for diagnostics are already in use, the French government is adamant that AI will not replace doctors, but assist them, e.g. by removing doubts and/or doing repetitive tasks. However, a need for doctors to embrace new technologies is recognised. Continuous education programmes for healthcare professionals will be put in place so that doctors are aware of the latest developments and can incorporate advances in AI into their practice, for patients to always have the best possible care. The specialties that are considered as the most likely to change quickly are radiology and dermatology.

There are several artificial intelligence systems under development in France for use in the healthcare sector. One tool already in use by accident and emergency departments is eCerveau (eBrain). This system links all essential information on bed availability, ambulance service and emergency department activity. The number of patients present in the service, and where they are physically, can be monitored in real-time. This enables extremely fine management of the resources of each emergency department, as well as optimal orientation and management of patients during periods of stress or crisis.

The department of social security has a joint research project with the Ecole Polytechnique to exploit and analyse data from all the different regional social security regimes to detect abnormalities in drug use, fraud and abuse. This will also create a database that can be used for epidemiological studies and help politicians in the construction of future public health policies and improve the efficiency of the social security department.

Doctors at the Trousseau hospital in Paris have a developed an intelligent system for obstetrics and gynaecology ultrasound imaging. A preliminary study has evaluated the system's ability to support accurate annotations of ultrasound images, using ultrasound diagnosis of ectopic pregnancy as a model clinical situation. The precision rate is appropriate for accurate input of a computer-based clinical decision support and it is hoped that it will eventually be used to support medical imaging diagnosis of complex conditions in obstetrics and gynaecology.

A project on-going since 2010 is the development of software that can read and summarise patient data rapidly in order to provide the emergency services with the information they need to make instant decisions e.g. prescribed medication, comorbidities etc.

There is also a current French-led H2020 project, Desiree, which is a web-based software ecosystem for the personalised, collaborative and multidisciplinary management of primary breast cancer. Desiree will provide decision support on the available therapy options by incorporating experience from previous cases and outcomes, going beyond the limitations of existing guideline-based decision support systems (DSS).

With all these examples, one potential bottleneck is the quality of the data in the system. While the medical database is a nationwide resource it was originally constructed with the aim of determining costs therefore sometimes specific incidences are not completely annotated e.g. if a patient was hospitalised for a respiratory problem the fact that they also had cancer might have been overlooked as it did not contribute to the expenses incurred. Correction of these errors is an important on-going task.

There is no doubt that AI has the potential to revolutionise healthcare. It is clear that tasks that today are only performed by a doctor will one day be carried out by a medical technician or even a computer interface. This is why education of doctors and the general public about the place of AI in healthcare has such prominence in the French government's plan.

Will algorithms predict the future soon?

Experts debate AI's predictive potential

'Hello, John? You are about to suffer a heart attack – please come to the hospital immediately!' Will we, one day, be collected by emergency doctors even before we're ill? If it was up to some AI experts at Medica 2018, this could be the case – soon. Held during the event, the Health IT Forum examined the predictive potential of artificial intelligence – although some obstacles must be overcome to achieve perfect AI predictions.

Report: Wolfgang Behrends

Big data, deep learning, robotics – in recent years medicine has progressed enormously in all these areas, but prognoses on future technology are difficult. Yet, during Medica, some IT experts ventured to gaze into a crystal ball. The group included:

- Pradeep Walia, cofounder and director of Artelus
- Matej Adam from Watson Health Executive EMEA, IBM
- Dr Björn Schreiweis, Research Associate at the Institute for Medical Informatics and Statistics in Kiel University
- Jaakko Nurkka, cofounder and CEO of Cliniserve
- Dr Stefan Heinemann, Professor for Business Ethics at the FOM University of Applied Sciences for Economics and Management Essen and spokesman of the Ethics Ellipsis Smart Hospital, Essen University Hospital.

Initially, the moderator Professor Tobias Daniel Gantner, CEO of Healthcare Futurists, spoke about the main scientific driver: curiosity. 'Researchers have always wanted to know why things happen the way they happen. Models based on big data could make this possible in a very novel way.'

Machine makes humans human again

However, gathering as much data as possible to send it through an algorithm is not quite the best way, Schreiweis pointed out: first we need to find out which data really helps us if we, for instance want to predict heart attacks. 'Even now, one of the most important tasks is to reliably navigate through the sheer mass of data and to distinguish between important and unimportant information, Adam agreed. 'If we succeed with this, artificial intelligence can take on many tasks. Doctors and nurses would finally have more time to concentrate on the human aspect of their work.' This centres mainly around the elimination of administrative tasks, which still make up a large part of the workload, Nurkka added.

A lively discussion around the predictive potential of artificial intelligence (from left): Moderator Tobias Daniel Gantner, Pradeep Walia, Matej Adam, Björn Schreiweis, Jaakko Nurkka and Stefan Heinemann. Photo: Behrends

However, there is a long way to go until then. 'It will take another 20 years until we'll actually have enough relevant data to reliably differentiate between correlation

Spatial cognition in aging and neuro-degeneration

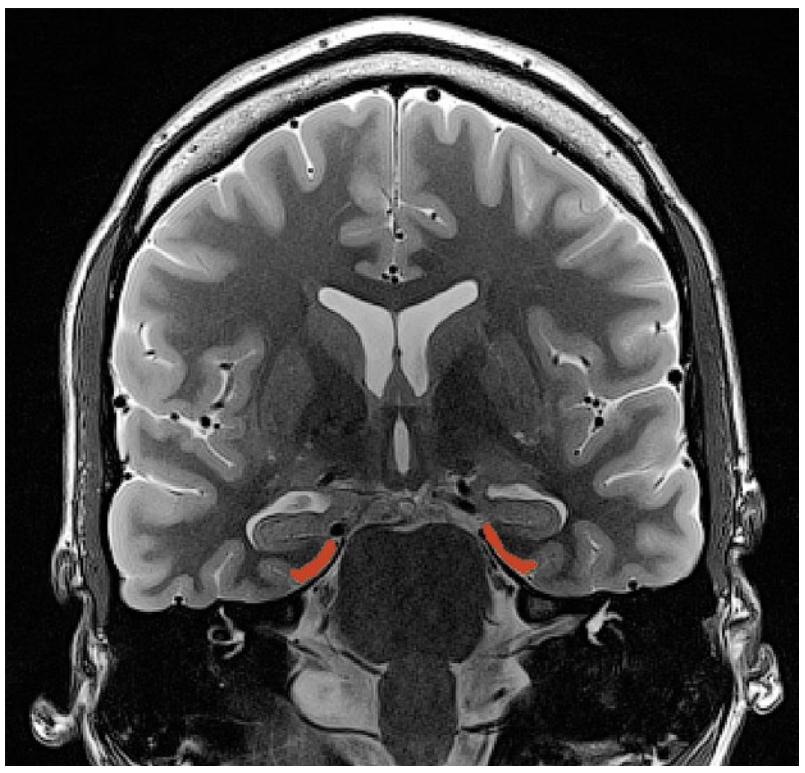
When the compass fails

Where are we coming from? Where are we going? Where are we right now? Our sense of spatial orientation - a complex interaction of various cells in the brain - gives us answers to these questions. In November 2018, around 70 experts in Magdeburg discussed changes in this navigation system induced by age and illness at the 'Interdisciplinary Symposium on Spatial Cognition in Aging and Neurodegeneration' (iSCAN). Professor Thomas Wolbers, one of the organisers, spoke with us about the problems of diagnosing orientation disturbances and how the measurement of our sense of space could help in the fight against neurodegenerative illnesses such as Alzheimer's.

Report: Wolfgang Behrends

'In our brain there are several cell types that code spatial information,' explains Wolbers. The so-called place cells in the hippocampus and grid cells in the entorhinal cortex process the current position in the space – in principle similar to the GPS in a navigation system. Other cells function like a compass, sending signals to the head as to which direction it is oriented at any given time. This collective spatial knowledge is used by the brain to coordinate motoric impulses and thus to steer the movement of the body from A to B.

Just like a compass that no longer points North reliably after several shocks, even this orientation centre in the head can malfunction: 'Due to brain damage in the regions where these types of cells are located, patients can develop very specific orientation disturbances.' Using functional magnetic resonance imaging (fMRI), these disturbances can be rendered visible: Changes in the blood's oxygen content exhibit the activity of certain brain areas in the form of voxels (spatial pixels). 'Thus we can recognise signals transmitted by grid cells when traversing a space,' Wolbers explained. If there is a disturbance in the sense of orientation, then these signals appear as distorted or temporally unstable. 'That shows that the cells are no longer able to precisely compute the position in space.'



In the entorhinal cortex (red) the brain processes the current position in space. This region is particularly vulnerable to age-related and illness-induced degeneration, which can lead to orientation disturbances.

The vicious circle of deterioration

The most important disturbance factor is aging, Wolbers pointed out. 'When we age, different neuronal deterioration processes occur in the brain. Some of the regions, like the entorhinal cortex, are particularly vulnerable to such deterioration. Thus the spatial orientation capacity declines successively with age.' Usually the disturbances occur first in unfamiliar environments, for example on vacation; later orientation becomes increasingly difficult even in familiar places. 'This leads many senior citizens to adopt an avoidance attitude, so they are almost unable to move beyond their own homes. This again promotes cognitive deterioration – a vicious circle.'

Illnesses can further accelerate this disorientation. 'The best known example is certainly Alzheimer's disease. Here abnormal tau proteins are deposited in the brain that can restrict the functionality of the nerve cells – and thus also cognitive performance. In some six in 10 Alzheimer's patients this illness also has an impact on orientation – they get lost frequently, don't find their way home without help anymore.' Depending on which brain region is affected, even a stroke can restrict the compass in the head, just as much as psychiatric illness such as schizophrenia.

Using VR for standardised orientation tests

While the activities of the sense of orientation can be shown using fMRI, the diagnosis of the disturbances is still difficult due to a lack of standardised tests. 'That ought to change in the coming years,' the neuroscientist hopes. 'There are several groups working on the development of tests by which it is possible to evaluate the seriousness of orientation disturbances.' One of the key technologies here is virtual reality (VR): If the person being tested is given the task with 3-D visors to find his way in a virtual space, then much data is generated that can be evaluated that allows measurement of the kind and degree of disturbance. Possibly VR may even be used for therapy in cases of orientation disturbances. But there is still a long way to go before this is possible, Wolbers believes.

During the recent iSCAN Symposium, early recognition of cognitive deterioration processes was also strongly debated. A uniform standard to measure orientation disturbances could also serve as a significant prognosis marker. 'Alzheimer's has a degenerative effect', Wolbers noted. 'This means that the illness has already been progressing in many patients for 10 to 15 years before the first diagnosis is made. Currently there is still no therapy. But, when a treatment is developed, it is of enormous importance that the signs of the illness are recognised as early as possible. Disturbances in the sense of orientation could be such an indicator.'

Source: Shutterstock/Nizwa Design

Professor Thomas Wolbers heads a working group at the German Centre for Neurodegenerative Illnesses (Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE)) in Magdeburg and is among the organisers of the 'Interdisciplinary Symposium on Spatial Cognition in Aging and Neurodegeneration' (iSCAN). A specialist in age-related and illness-induced changes in cognition, his research investigates neurodegenerative processes, the development of standardised neuropsychological diagnostics and training methods to avoid neuronal deficit as well as the restoration of cognitive functions.

and causality in data patterns,' Schreiweis observed. Current scepticism towards artificial intelligence is understandable, but unfounded, said Walia: 'When MR imaging was first introduced, most experts were also sceptical – but now you couldn't imagine medicine without it. Medics who deny the potential of artificial intelligence will become obsolete one day.'

They have no bread? Give them artificial intelligence!

The potential of artificial intelligence is vast, and not only for medicine, Walia confirmed. But before the technology can be introduced comprehensively some very different issues must be addressed. 'There is no point in convincing someone of the advantages of artificial intelligence if that person does not have enough food to live on.' Education is a decisive prerequisite required to enable people to handle new technology. An important part of technological progress is to design systems in such a way that they can be used with ease and intuitively, emphasised Nurkka.

Anonymous health data – an illusion?

People need to understand the importance of personal medical data, Heinemann said. 'These days, companies think of health data as a resource – but this view hinders technological progress. We need free access to anonymised health data to train algorithms.'

But, this is where the problem lies, Schreiweis countered, because real data anonymity is an illusion: 'When sufficient data sets are available, algorithms can match individual data to individuals.'

Companies such as Google support hospitals with generous donations, Walia noted. This facilitates important progress, from which everyone will benefit ultimately. However, in return their money buys them access to research – and health data – which they use to their own advantage.

Adam put it in a questioning nutshell: 'How do we facilitate the secure handling of personal health data without limiting access to data sources?'

Hope for a better future

To really utilise the enormous potential of AI in medicine, we need a system which does not view the data as a commodity, Heinemann added. 'Then everyone would have access to the treatment they need, independent of their financial situation.' Nurkka and Adam were equally confident – assuming that data was to be liberated from its proprietary silos in companies or hospitals and made available widely. 'We just need to connect the data points,' Adam concluded. 'Then we have all the information we need for better healthcare.'

Immuno-oncological biomarkers in cancer

Seeking to augment TILs value

Measuring tumour infiltrating lymphocytes (TILs) is gaining importance in immunotherapy, but other variables must also be considered to boost prognosis and prediction accuracy, a leading pathologist argued at EBCC 11 last March in Barcelona.

Report: Mélisande Rouger

When it comes to prognosis and prediction for immunotherapy, a potentially new variable is emerging – tumour infiltrating lymphocytes (TILs) – white blood cells that have left the blood stream to migrate towards tumours and that have always been present in the tissue from where the cancer originates. These can be assessed on haematoxylin and eosin-stained (H&E) slides, and therefore are a marker that can easily be assessed by pathologists worldwide, since only a microscope and one H&E-slide need to be used, Belgian pathologist Roberto Salgado pointed out.

'In general, TILs and immune signatures in breast cancer are strongly correlated,' he explained. 'The question is: How can we define added clinical value for TILs with H&E and do we need additional variables, such as immune signatures – and, if yes, how should we use these?'

TILs and PDI mRNA signatures make up a chemotherapy response map

Carsten Denkert, a leading pathologist from the Charité Hospital in Berlin, combined the number of TILs and PD1 mRNA signatures in what he described as a 'chemotherapy response map'. In this context, quantity clearly matters, Salgado pointed out. 'If you have a lot of TILs and PD1 mRNA signatures, your results are excellent. But there is this middle category of TILs with intermediate scores, which is a bit blurry and difficult for pathologists to assess. The question remains of how and whether we should combine these two variables in order to define predictive accuracy of treatments.'

The time is right to use TILs in clinical trials design

The idea of using TILs as a biomarker is gaining weight among pathologists, and evidence on clinical utility is emerging. The moment has come to use TILs in clinical trials and assess even combinations of TILs with immune-gene expression signatures in future clinical trials design, Salgado argued.

In a recent study associating TILs with anti-PD(L)-1 response, Salgado and co-researchers demonstrated that a high number of TILs in the metastatic setting means treatment is working, independently from all other variables.

'If you have metastatic BC and a lot of TILs, you do excellently in terms of response,' he explained. These results were confirmed in another study on TILs in a nivolumab mTNBC-trial from the Netherlands Cancer Institute (NCI).

The combination of variables seems to be key to enhance accuracy, since patients who have extremely high number of TILs may not all respond to treatment and we need to be able to identify these. Salgado suggests using, for instance, TILs in alliance with genetic profiles to identify these patients.

Neoadjuvant setting is quite an opportune moment to predict which patients will present pCR (pathological Complete Remission, i.e. the complete disappearance of cancer after treatment) after chemo + anti-PD1, evidence shows.

'We do know that if you just give chemotherapy and perform a biopsy after treatment, most of TILs go up. This is also the case in neoadjuvant setting,' he said. 'We will have more information available at next major cancer meetings.'

Residual Cancer Burden - measuring remaining cancer

An important question that clinicians must also answer is how to use this information. They should probably consider adding RCB – Residual Cancer Burden, i.e. a measurement of the amount of cancer left after treatment – as an endpoint including the number of TILs, Salgado believes.

'Can we identify either preoperatively this subcategory or, and this is emerging, can we develop so-called post neoadjuvant trials, in which we can stratify this patient population into treatments on high TILs and RCB with an immune checkpoint and without, depending on the amount of cancer left after treatment?'

Professor Michail Ignitiadis, from the Jules Bordet Institute, recently conducted an enlightening trial in patients receiving trastuzumab/pertuzumab based chemotherapy in the neoadjuvant setting (TRYPHAENA sub study). The results revealed that having a high number of TILs at baseline is a good indication that treatment is working, whereas having a low amount of TILs translates into a worse prognosis. 'This shows we need this combination of markers, of both a measure of disease after treatment and TILs in this case,' Salgado pointed out.

Having a lot of TILs and gene expression profiles is good news

The combination of TILs with gene expression profiles can outline three types of categories of response, all triggering different questions.

'Having a lot of TILs and gene expression profiles is good news; yet can we do even better in terms of enhancing immune reaction?

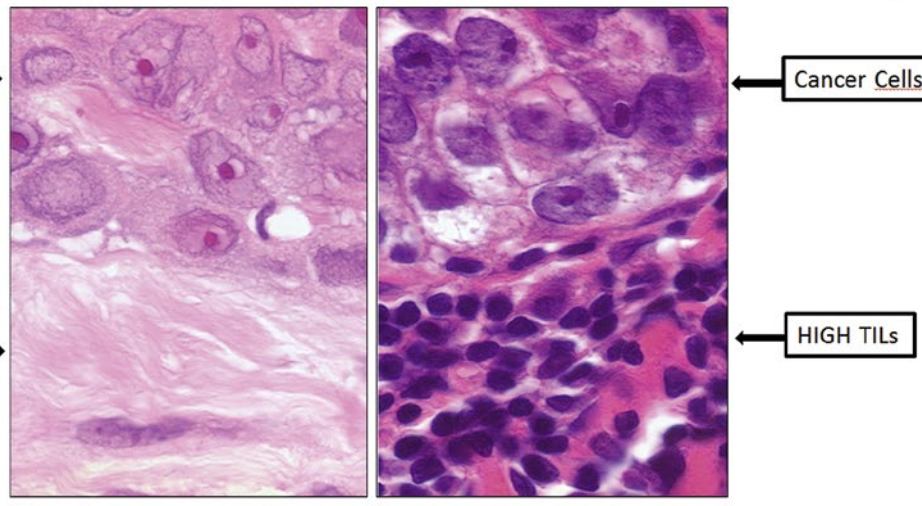
'And, if you have a low number of TILs and low expression profiles, how can we enhance the immune system? As for having a lot of TILs and intermediate gene expression, or vice versa, we don't know what to do with this category. However, these are the majority of our patients,' Salgado said.

TNBC: Triple Negative Breast Cancer

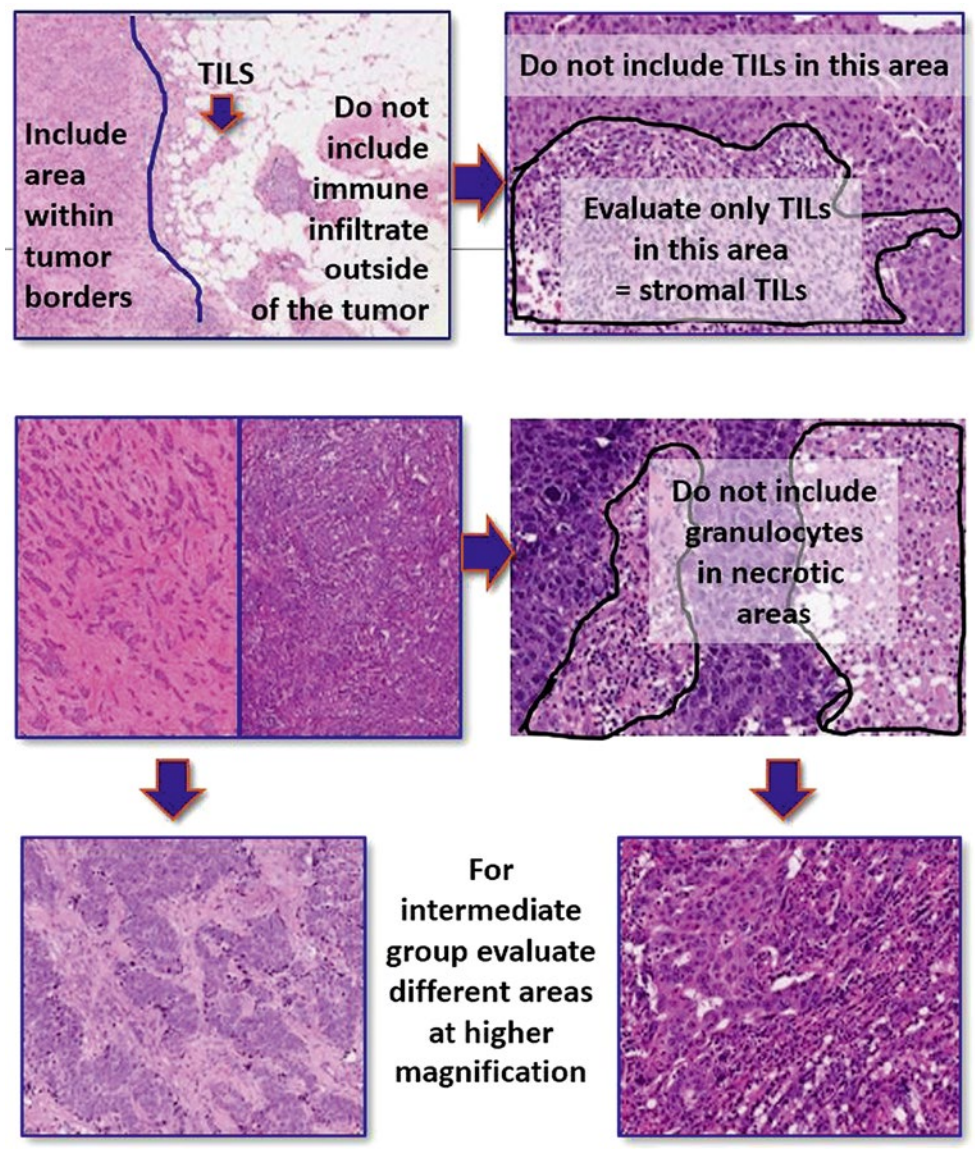
Eventually, TILs must be combined with something else to improve prognosis. In a recent study carried out in a pooled analysis of phase-3 clinical trial in patients with TNBC (Triple Negative Breast Cancer), Salgado and co-researchers have combined TILs and nodal status by tumour size and age. 'We could accurately define five years of survival of these patients. But what do we do with this information? This is challenging, arguing that this information can be used to develop clinical trials testing, for example de-escalating treatment options,' he said.

Prediction, defined as predicting response to a particular treatment may require multiple sources of information. 'When you have a high number of TILs, you have good response, but,' he concluded. 'you will obtain higher accuracy combining TILs with something else, for instance LDH concentration.'

Roberto Salgado is an anatomic pathologist at Department of Pathology in GZA/Antwerp, Belgium. He is also a scientific collaborator at the Breast Cancer Translational Research Laboratory in the Jules Bordet Institute, the Immuno-Task Force of the Breast International Group and the Translational Breast Cancer Genomic and Therapeutics Laboratory of the Peter Mac Callum Cancer Centre in Melbourne, Australia. He chairs the International Immuno-Oncology Biomarkers Working Group, an international consortium of pathologists who develop guidelines and guidance on the assessment of immuno-oncological biomarkers in cancer. Salgado works in close collaboration with the EORTC and is an auditor on molecular pathology/genetic laboratories for the federal Belgian government.



Salgado_2: How to score TILs?



(Source: Salgado et al., 2015, Annals of Oncology / Denkert et al., 2015, Modern Pathology)

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SPECIAL ISSUE FOR THE EUROPEAN CONGRESS OF RADIOLOGY

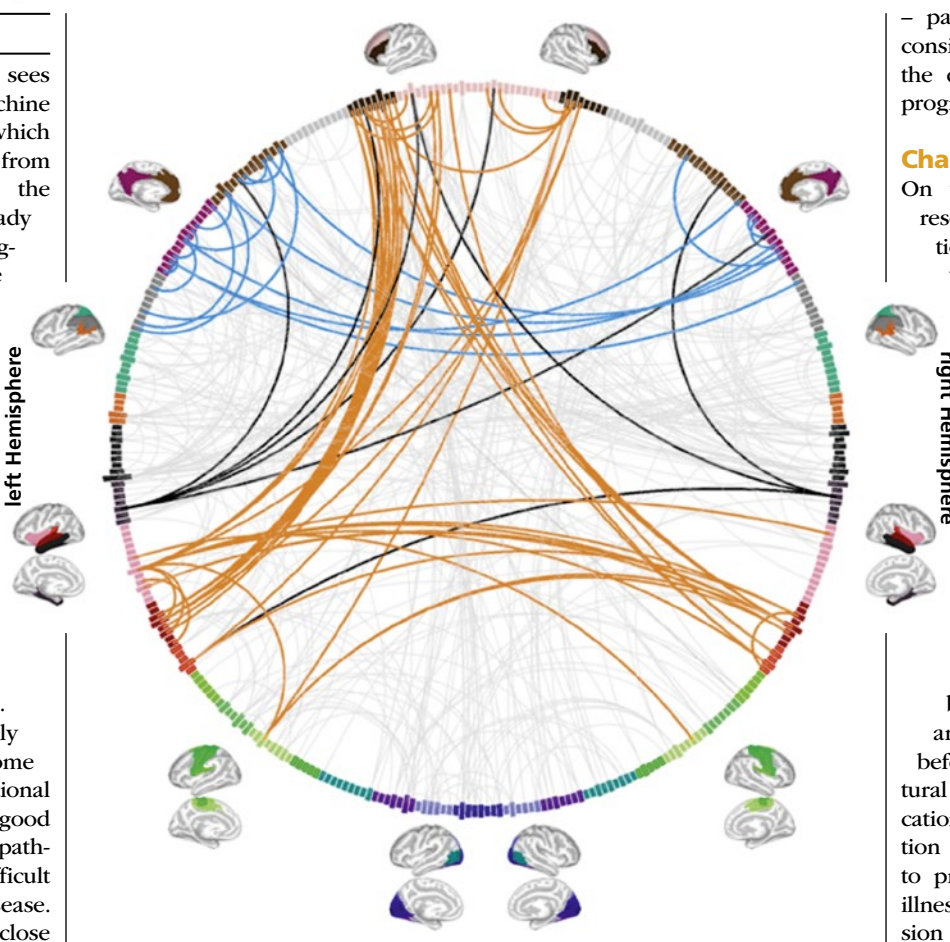
VIENNA • AUSTRIA • FEB 27 – MAR 03 2019

Man and machine: today's centaur

Artificial intelligence continues to drive radiologists' discussions. Among them, Associate Professor Georg Langs, head of the Computational Imaging Research Lab (CIR) at the University Clinic for Radiology and Nuclear Medicine at the Medical University of Vienna, believes: 'The evaluation of patterns in data from imaging examinations and clinical information about patients using machine learning will change fundamentally our understanding of illnesses and their treatment as well estimation of their course.'

Report: Michael Krassnitzer

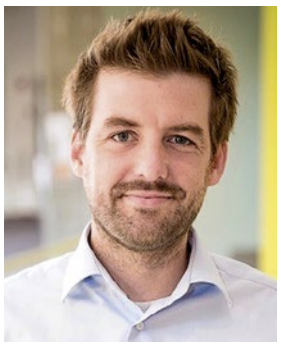
The Austrian computer scientist sees two major applications for machine learning – the form of AI by which a computer program learns from a mass of examples. First is the automated recognition of already familiar patterns, markers or signatures in image files that are diagnostically relevant, that also help to say something about the future course of an illness or, for example, how a certain patient will respond to a treatment. This also includes even the search for small tumours or metastases. The second application – and in Langs' view perhaps even more promising – is the discovery of new patterns, markers or signatures of diagnostic relevance that have yet to be identified. 'Machine learning delivers really good results where we have come to a dead end using conventional markers,' Langs emphasises. A good example is the diagnosis of idiopathic pulmonary fibrosis (IPF), a difficult to diagnose and rare lung disease. Here Langs' research group, in close cooperation with the lung fibrosis specialist Professor Helmut Prosch at the Vienna's University of Medicine, identified six – among a total of 20 – patterns in CT lung images that consistently change in the course of the disease and can be applied to prognoses for the disease.



The changed connectome in patients with epilepsy of the left temporal lobe. There is a global change in both the speech network (orange) and, to a lesser extent, the default-modenetwork (blue). The lines show the sub-network where a reduction in connectivity arises in connection with the illness. (Figure: Karl-Heinz Nenning)

Changes in the brain

On the basis of MR images, the researchers studied how the functional connectivity architecture in the brain changes in patients with epilepsy or a glioblastoma. Although these diseases are based on focal lesions, the complex networks formed by the neurons change in the effected patients throughout the entire brain. 'These are plasticity mechanisms that are candidates for markers with which structural changes can be recognised earlier,' explained Langs. Initial findings indicate that this image analysis of brain function can be so sensitive that these mechanisms are recognisable even before a lesion is visible in structural MR images. With all these applications the aim is to create a prediction model that makes it possible to predict the future course of the illness. 'However if a treatment decision is made based on such a model, it must be clear what the underlying mechanism is,' Langs emphasises. Machine learning is 'agnostic', as the computer scientist puts it: in a mass of examples it recognises a pattern that changes consistently and uses this – without regard for whether this pattern coincides with familiar physiological processes. If such a pattern is identified, then the computer scientist passes the ball back to biological research. 'Meanwhile, this Ping-Pong game between radiologists and machine learning experts works very well and leads to progress in the understanding of both sides', Langs points out.



Associate Professor Georg Langs (Dipl-Ing) studied mathematics and computer science in Vienna and Graz. Following years of research at the Ecole Centrale in Paris and the Massachusetts Institute of Technology (MIT) in the USA, the computer scientist returned to Vienna's Medical University (MedUni Wien), where today he heads the Computational Imaging Research Lab (CIR, www.cir.meduniwien.ac.at). He also teaches at the University of Vienna, is a reviewer for several international specialty journals, including IEEE Transactions on Pattern Recognition and Machine Intelligence and IEEE Transactions on Medical Imaging, and is the author of numerous technical articles.

AI is a black box

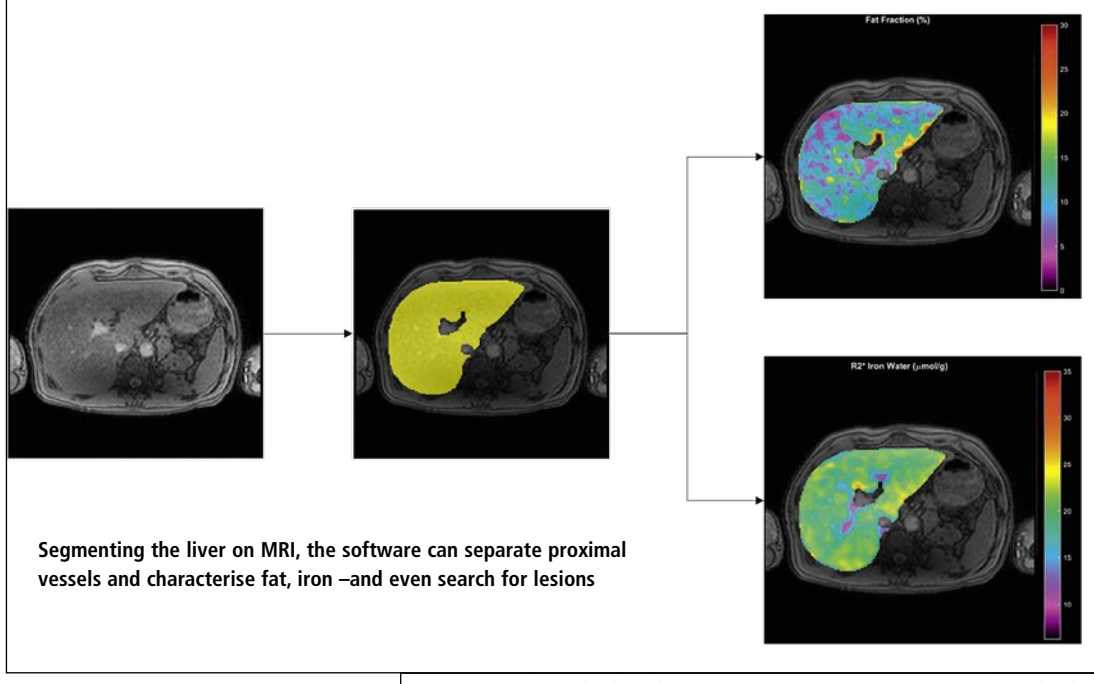
scientists are also trying to manage the so-called 'Black Box problem' – that it is impossible to trace from outside how a program based on

Continued on page 6

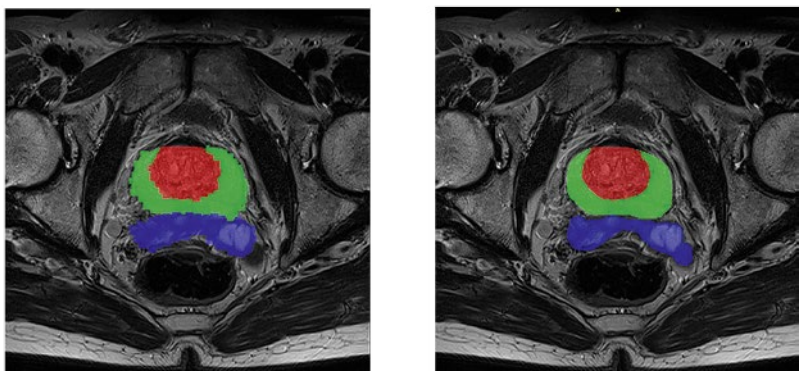
Expediting image analysis in radiology and pathology

For AI the time has come

AI has made an extraordinary qualitative jump, particularly in machine learning. This can help quantify imaging data to tremendously advance both pathology and radiology. At a recent meeting in Valencia, delegates glimpsed what quantitative tools can bring to medical imaging, as leading Spanish researcher Ángel Alberich-Bayarri unveiled part of his work.



Segmenting the liver on MRI, the software can separate proximal vessels and characterise fat, iron –and even search for lesions



The QUIBIM image analysis platform uses deep supervision to generate output segmentation masks combining multi-layer and multi-resolution information

Report: Mélisande Rouger

The boom in companies and start-ups developing AI for tasks that impact on healthcare, and particularly pathology and radiology, is not about to fade. However, many have not looked at this potential properly, according to Alberich-Bayarri, scientific-technical director of the Biomedical Imaging Research Group (GIBI230), speaking during the Triangle meeting in January. 'The time has come to discuss these things properly,' he said.

Alberich is CEO of QUIBIM, a spin-off company of La Fe Polytechnics University Hospital. The group develops machine learning tools to quantify imaging data, most notably a platform for quantitative image analysis and structured reporting capabilities, which has just received CE Mark certification as class IIa Medical Device for imaging biomarker analysis algorithms, zero footprint DICOM viewer and platform hosting these components and medical imaging data.

The four pillars of radiology acceleration

'Quantification of imaging data is a sector that has a very high potential in clinical research studies, because AI, in this setting, can be used to speed things up considerably,' he explained.

QUIBIM works to accelerate workflows in pathology and radiology along four main axes: image reconstruction, segmentation, detection and data mining.

AI could help significantly to reduce acquisition times, for example in MRI examinations, by using raw data generated by the imaging modalities. Image reconstruction is currently the main focus of investigation, and Alberich works on algorithms that process data using deep learning for under-sampled MRI reconstruction. 'Our aim is to identify all these regions, tissues and their potential variability. It would be a great advance,' he said.

The research community is experiencing a new paradigm, in which they receive all sorts of imaging data and aim to extract characteristics on shape, volume, texture, diffusion, etc. 'We need to integrate all the data to be able to extract and mine information that we don't know yet, to discover, for instance, new biomarkers giving an answer to unsolved clinical questions.'

A game-changing new neural network for segmentation

One of the bottlenecks right now is segmentation, but this brand new area will greatly benefit from AI, Alberich believes. 'Many engineers choose to subspecialise in segmentation right now, compared with, say, image registration because, as a new field emerges, new questions are raised and there is room for improvement,' he said.

In coming years, every work process including medical imaging will have to implement AI based segmentation because it will help save large amounts of time.

The U-net, a convolutional neural network that was developed for biomedical image segmentation at the Computer Science Department of the University of Freiburg, Germany, has been a real game-changer in segmentation and more generally radiology, Alberich explained. 'The network's modified architecture elegantly outperforms its predecessor, the sliding-window convolutional network,' he said, 'and the U-net can work with fewer training images, yet yield more precise segmentations,'

QUIBIM also uses deep supervision to generate output segmentation masks combining multi-layer and multi-resolution information. 'Most of the critics on AI now target so-called 'black box' solutions, with one entry point and one exit point. So, an interesting line of work for us now is to get as much information as possible on the network's dark layers to improve results and make the tool more understandable,' Alberich explained.

More perspectives lead to better insights

Segmentation techniques have already improved cartilage diagnosis, a service that was long confined to few specialised centres. 'It used to take a biomedical engineer hours to segment the cartilage manually, and then parcel and calculate its properties,' he pointed out. 'Now the whole process is much faster and similar to virtual arthroscopy, which can be of value to orthopaedic surgeons. So we're very interested in this potential.'

Alberich and his colleagues are notably working to label images in all planes, to improve results. 'There may be errors in the liver when using only one network, which has been trained with either transversal, sagittal or coronal images. But when we combine all the information and generate a tissue probability map, liver segmentation is almost perfect,' he explained.

In detection, once the structure and organs are visualised, it can be interesting for the pathologist to use clustering techniques – either supervised or non-supervised AI clustering. Both techniques can be useful, depending on the application. Non-supervised AI clustering can for example help extract new quantitative information and acquire more knowledge.

The human mind is unable to visually study patterns in patient variation over time, and to group patients based on these criteria. Agglomerative hierarchical clustering could help in this regard, by helping to evaluate response.

'Non-supervised AI can help unveil and extract information that we are not yet able to see on imaging,' he added. 'It can be very useful in these patients. Working with a set of variables is very good for recurrence prognosis in baseline diagnostic studies.'

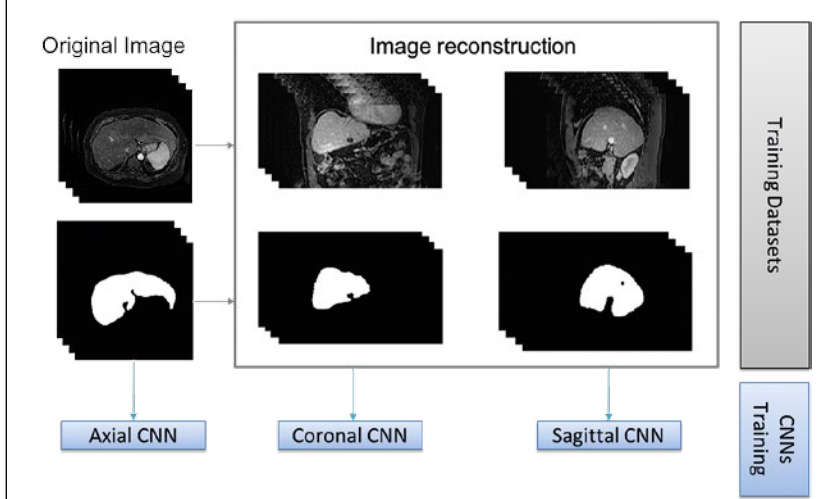
Biomedical engineer **Ángel Alberich-Bayarri PhD** is scientific-technical director of the Biomedical Imaging Research Group (GIBI230) at La Fe Polytechnics University Hospital and CEO of the spin-off QUIBIM, in Valencia, Spain. He is board member of the European Society of Medical Imaging Informatics (EUSOMII) and of the European Imaging Biomarkers Alliance (EIBALL). With over 10 years of experience in the development of quantitative image analysis solutions and their integration in clinical practice, he has co-authored more than 50 research papers and participated in more than 10 international medical imaging research projects.

Man and machine: ...

Continued from page 5

machine learning arrives at its results. 'In the past two years efforts have been intensified to develop methods for tracing the prognosis back to the source,' Langs reports. Thus, the following question is answered: *What is presented in the data that leads to a diagnosis or a correct prognosis?* This information is also forwarded to the physicians so that they can investigate which physiological processes are behind everything. These efforts are summarised by the maxim 'Explainability'.

'The radiologist is increasingly becoming the data integrator and interpreter of subtle patterns in the diagnostic process – and machine learning is a powerful tool for this,' Langs explains when asked about the future of radiology, given the numerous AI applications in the field. 'Certainly, radiologists will not be replaced by machines but their work will change. In the future, they will be able to concentrate on more complex questions.'



Using combined information of transversal, sagittal or coronal images to generate a tissue probability map in liver segmentation

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Physicians buy worse but more affordable devices

Rads can become 'centaur radiologists'

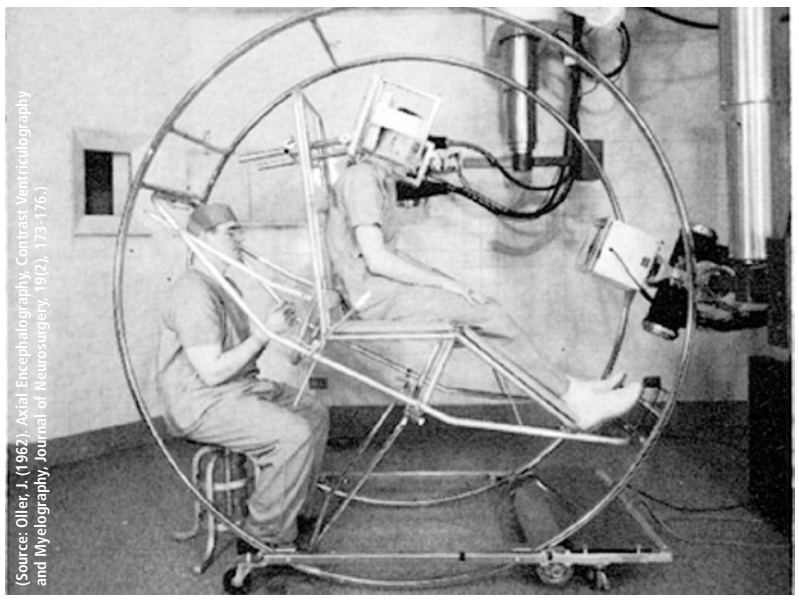
Technological change is a major part of change management in radiology and it is inevitable. Artificial intelligence (AI) has slipped into every area of life including the hospital, and is already making decisions in radiology systems. The good news is that radiologists could win on two fronts, provided they play their cards well, a leading USA radiologist told delegates at a recent congress in Spain.

Frank Lexa, a professor of radiology at the University of Arizona and recognised speaker on medical leadership, believes there is no way to stop the waves of change brought by disruptive technology including AI, but radiologists can learn to surf. 'AI already helps us with scheduling and with image display protocols. Stopping technologic change is not an option,' he told delegates at the Triángulo Radiológico meeting, held in Valencia in January.

Three types of technology have impacted on humans over the past hundred years. Incremental technology is an improvement of the existing technology and something of which radiologists are usually very fond. 'It's one of the reasons that I became a radiologist. Every year, things get better, CT scanners get faster, MR scanners have higher resolution and we obtain more information,' Lexa explained. 'But there is no change in customers and it doesn't displace any other technology.'

Transformative technology, on the contrary, is where one technology replaces another due to quality, performance and/or cost advantages. The cassette player, for example, replaced the vinyl record, and later was replaced by digital music.

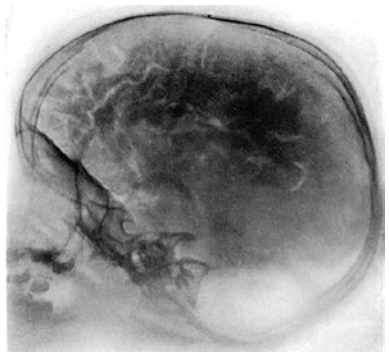
In radiology, many technologies have replaced others in the blink of an eye (5-10 years). The pneumoencephalogram is something most radiologists have never heard of, yet it was all the rage just over 40 years ago.


(Source: Oller, J. (1962). Axial Encephalography, Contrast Ventriculography and Myelography, Journal of Neurosurgery, 19(2), 173-176.)

An axioencephalography chair and cassette holder

'It looks like somebody who is training to be an astronaut. In the US, CT almost immediately replaced the pneumoencephalogram. Some people used it for amusement through the holidays, but they were no longer using it for patients. In the space of a couple of years, it was completely replaced,' Lexa pointed out.

AI is part of disruptive technology, which, as first described by Clayton Christensen and Joseph Bower from Harvard University (Disruptive Technologies: Catching the Wave, Clayton Christensen and Joseph Bower, Harvard Business Review, 1995), consists of adopting an innovation that is lower cost and lower quality. 'It's often worse quality, but it changes the market and expands it. Disruption changes who the market is and how you work,' Lexa explained.


Pneumoencephalography procedure: a roentgenogram of the head after an intraspinous injection of air

This happened to radiologists when imaging systems were developed for non-radiologists. Many ultrasound machines created recently have worsened image quality, but made the technology more available to all medical specialists. 'How many years did some people train, including myself, to learn how to use ultrasound? Now, it's like a stethoscope. Everyone who goes through medical training now thinks that they can do ultrasound; that's a true disruption,' he pointed out.

Another example is the extremity MR system, which produces worse images than a traditional MR scanner launched 20 years ago. Physicians buy worse, but more affordable equipment. 'You can put this anywhere. You don't need to block out the rest of the building; it's cheap, and means you can pretty much have MR wherever you want.'

A lot of disruptive technology gets better after some time. This is happening with ultrasound, small mobile CT scanners and, soon an MRI system, will fit in the back of a car, Lexa predicted. 'Anyone who doesn't believe me, anybody who wants to take that bet, I'll have dinner in Chicago with. Prepare for it!'

In spite of all the disruption, the traditional value that only the radiologist does the consultation, supervises imaging, interprets and does form of management has not been broken up. However, with AI tools improving at the speed of light, it's unclear whether radiologists will keep on playing this role. It's only natural that they feel threatened by AI. 'I'm scared by AI as well. It does make me wonder sometimes what we're training for,' Lexa exclaimed.

In the future, more and more machines that allow non-radiologists to do imaging will emerge, and also more machines that don't need a technologist to be used. Machines that provide a preliminary read are already available. Computer systems that can extract information from imaging scans that human eyes and brains can't easily see are also already available. Right now, in the USA, the most popular thing for residents is intervention, and part of this is the worry that it's going to be easier for software algorithms to do most of the rest of diagnostic radiology. However, robots will also assist or perform interventional procedures.

AI systems that can aggregate genomic imaging and clinical information are already available, and so are phone apps that will read a chest X-ray and AI systems that can do peer review for radiologists. 'If you don't like being reviewed by other humans, I don't know how much you're going to like being reviewed by a robot. This is not something that's deep in the future. This is all happening now.'

The challenge for radiologists is how do they deal with these new scenarios? First, they must face that issue.

Coming: a fast throughput scanner to fit all sizes

Disruptive innovations in molecular imaging

Molecular imaging is an exciting field for scientists who are willing to explore and innovate, prominent Spanish physicist José María Benlloch pointed out when he reviewed some of the most impacting and recent innovations in his portfolio during a meeting in Valencia, Mélisande Rouger reports.

'Our mission is to develop innovative sensitive and harmless medical imaging instruments for early detection of diseases and follow-up. We also work to create new minimally-invasive therapies based on physics mechanisms, and enable technology transfer to the industry,' said Benlloch, Director of the Institute for Instrumentation in Molecular Imaging (I3M).

Of late, Benlloch and team developed the first PET scanner for preclinical evaluation of small animals – a technology they transferred to Bruker, and which Stanford University now uses.

Another recent ground-breaking innovation is the PET/MRI scanner dedicated to brain examination developed by I3M within the MINDVIEW (Multimodal Imaging of Neurological Disorders) European Project.

The project aims to diagnose and treat schizophrenia, severe depression, and all mental disorders.

The new, high resolution PET/RF coil for simultaneous PET/MRI acquisition was originally designed for 7-T MRI, but soon upgraded to 9-T and 15-T at different sites across the world.

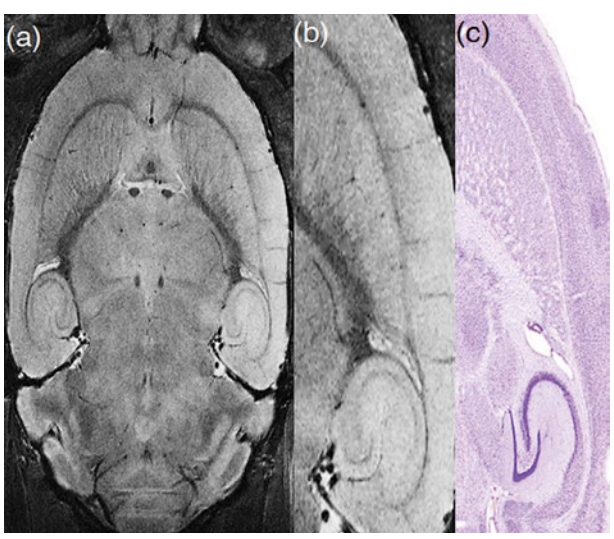
Benlloch believes this has tremendous commercial potential. 'There are about 40,000 MR scanners in the world, so the idea was simply to replace the radiofrequency device designed for brains to have an MR examination that also offers PET. Most MR examinations – perhaps over 40% – are for brain examination, so it makes sense to have such a solution,' he pointed out.

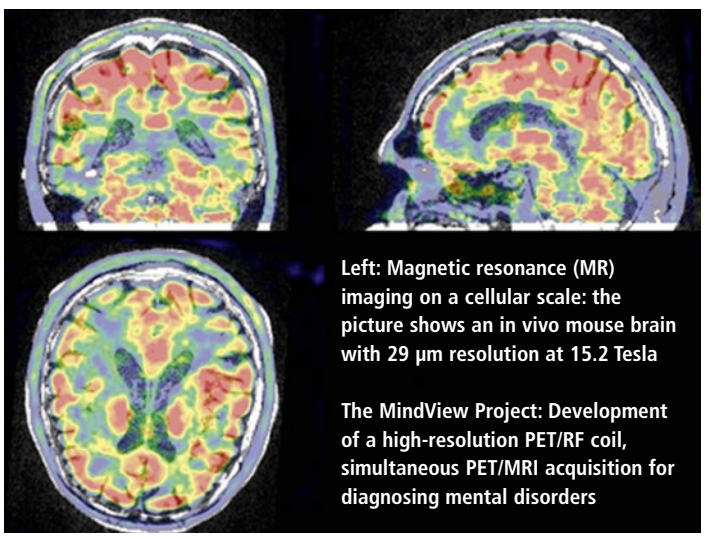
While working on the new machine, researchers found it must be adapted to accommodate a very large and heterogeneous population of patients. For example, the elderly with Alzheimer's may be challenging to image, due to age and condition.

In addition, many improvements must be made, starting with compatibility of the newly developed sensors with MR. 'These are silicon sensors that do not contain nickel, not to interfere with the magnetic field. Many of these sensors failed but images were obtained despite those errors. However, using appropriate software, the faults became almost undetectable. We even managed to obtain resolution lower than 2mm, which posterior solutions were unable to achieve,' Benlloch explained.

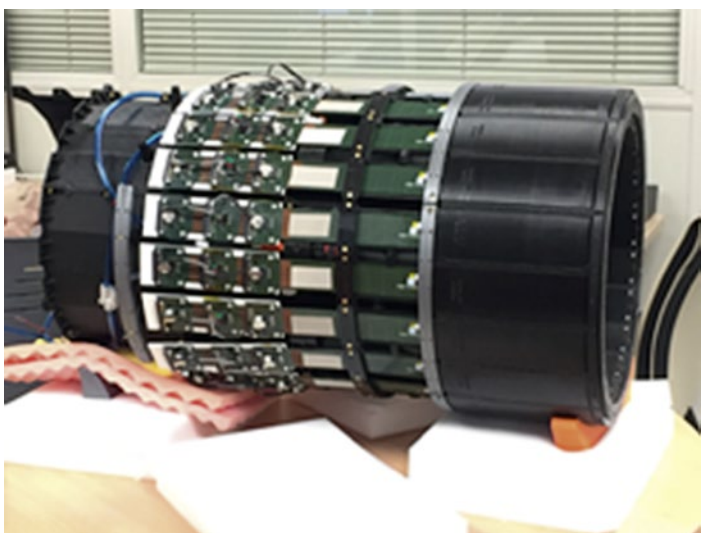
A while ago, I3M also created the innovative PET mammograph and new molecular compounds for early breast cancer diagnosis and evaluation of chemotherapy response, as part of the EU Mammography with Molecular Imaging (MAMMI) project.

The Mayo Clinic in Rochester, USA, installed the MAMMI Breast PET scanner for primary systemic neoadjuvant therapy, with excellent results. 'We could clearly see tumour extension reduction and reduction of glucose uptake after the first chemotherapy cycle,' Benlloch said.




Left: Magnetic resonance (MR) imaging on a cellular scale: the picture shows an in vivo mouse brain with 29 µm resolution at 15.2 Tesla

The MindView Project: Development of a high-resolution PET/RF coil, simultaneous PET/MRI acquisition for diagnosing mental disorders



Frank J Lexa MD MBA FACR is an academic neuroradiologist and currently a professor and Associate Chief and Vice Chair of Strategy and Leadership, in the Department of Medical Imaging at the University of Arizona. In his book 'Leadership Lessons for Success in Health Care' he takes a systematic approach to developing medical leadership skills.

'If rads don't face it, non-radiologists will. The choice for us, is change or be changed, disrupt or be disrupted, lead or be led,' Lexa advised.

Radiologists should make the most of disruptive technology. The optimistic solution will be to leave the sorting out of cases and eventually the boring cases to the computer, so that radiologists only read the interesting ones. 'A computer that ensures I don't make a mistake because it has high sensitivity, I would like that, particularly if it's late at night and if I'm working too many cases that day.'

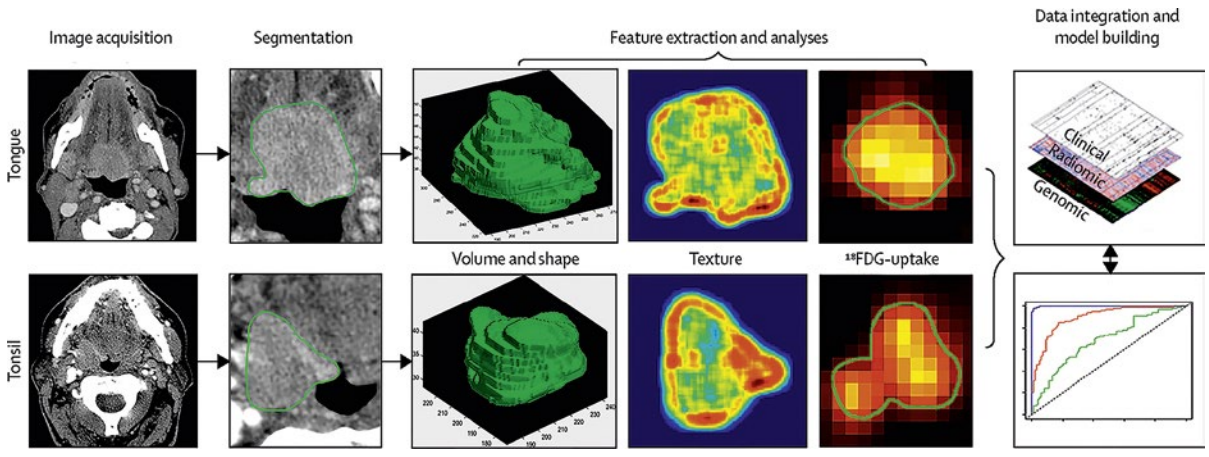
Rads can 'merge' with computers to become 'centaur radiologists', a combination that would help them have the best of both worlds. 'It's the notion where you have a horse's body and a human's upper body, a computer and a radiologist working together to read the images.'

Building value will prove essential to the task, and so will the attitude, Lexa believes. 'The future belongs to the brave.' (MR)

Distributed learning could be the way forward

Radiomics on tap in 5-10 years

Keeping data within the hospital by sending the learning modules to each hospital database might prove a game changer in radiomics, a leading Dutch researcher will demonstrate at ECR 2019



Radiomics, a field that aims to extract large amounts of quantitative features from medical images using data-characterisation algorithms, is a major advance for healthcare, according to Philippe Lambin, a radiation oncologist from Maastricht University.

'The information delivered by radiology, and more generally healthcare, is still based on a qualitative and semi-subjective assessment. There aren't that many quantitative data in the radiology report,' he pointed out.

Radiomics will help to remedy this situation by enabling the extraction of quantitative and measurable information on intensity, shape and texture of tumours, plus wavelengths, and complex semantic features that can represent frictions, for instance contact between a tumour and the bone.

15,000 to 20,000 quantitative image characteristics can be generated with radiomics to show gene mutations, differentiate aggressive from non-aggressive tumours, and assess treatment response. The histological type of the tumour can also be determined by mining biological information from a CT scan.

Within five to ten years, every hospital will use a radiomics solution, Lambin believes. 'A genomic signature means taking and sending a tissue sample to a lab. Extracting information from an already existing image is cheaper and much more attractive. Also, a biopsy may not represent a tumour's evolution over time. All these issues disappear with radiomics,' he said.

In the meantime, there are still major obstacles to its implementation in clinical practice, and radiomics algorithms must be rigorously validated and fulfil an unmet clinical need to pay off. 'Radiomics, today, is in a chasm – the valley of death,' Lambin said to describe the gap between scientific validation and applications in clinical routine.

Overcoming data confidentiality legislation

To be adequately trained, algorithms must be fed huge amounts of data from millions of images from different countries. Collecting these images and sharing the data is an issue, with all the existing data confidentiality legislation.

Sending the learning modules to each hospital database, instead of having the hospital send their data into a centralised system, would enable that difficulty to be overcome, Lambin believes. He and his team at Oncoradiomics, a Maastricht University spinoff, have developed such a solution, which they have called 'distributed learning from federated databases'.

'The benefit is that hospitals keep their databanks within their systems, which are protected by firewalls, rather than centralising the multiple databases from different countries,' he said.

The researchers already tested distributed learning at various locations across Europe and the USA, with results as good as software centralising data.

Another condition for radiomics to be implemented in clinical practice is to use quality research. A quality score to assess studies is available on the radiomics.world website, which guarantees enough patients are involved without external validation.

Lambin recommended using the TRIPOD classification to assess qual-

Continued on page 11

Philippe Lambin is a clinician, radiation oncologist and pioneer in translational research, with a focus on hypoxia and Decision Support Systems. He has a PhD in Radiation Biology. In 2016 and 2018 he was an 'ERC advanced & ERC PoC grant laureate'. He is also co-author of more 450 peer reviewed scientific papers (Hirsch Index) Google scholar: 86. A co-inventor of more than 18 patents, of which five are in the (pre) commercialisation phase, he has also co-promoted over 50 completed PhD's. Lambin is among the creators of 'Radiomics' (animation: http://youtu.be/Tq980GEVP0Y) and 'Distributed learning' a revolutionary Big Data approach for healthcare (http://youtu.be/ZDJFOxpwqEA, visit www.eurocat.info).

Professors José Benlloch (left) with Jerome Friedman, 1990 Physics Nobel Prize winner and his former mentor at MIT

José María Benlloch Baviera is Professor of Physics at the National Spanish Research Council (CSIC) and Director of the Institute for Instrumentation in Molecular Imaging (I3M) in Valencia, Spain.

He worked at the Massachusetts Institute of Technology (MIT), under the aegis of 1990 Physics Nobel Prize winner Jérôme Friedman. Benlloch has published more than 290 articles in scientific reviews, coordinated around 30 investigation projects and holds 15 patents. He has also created three spinoff biomedical engineering companies.

The EXPLORER total-body PET scanner, released in 2018 and originally conceived by Simon Cherry and Ramsey Badawi from UC Davis, is an inspiring advance. 'The Explorer has produced exceptional images. I have never seen such high-quality images in a commercial setting,' Benlloch confirmed.

Chinese radiologists have widely purchased the scanner, which enables image-capture of the human body in under a second. However, Western counterparts have not shown the same enthusiasm yet; they tend to prefer big scanners that can accommodate every patient, even though these are not cost-effective enough for private practice, Benlloch believes. 'We are going to develop something to interest everyone, i.e. a scanner that can accommodate every patient and has a high turnover – imaging many patients in an hour.'

Having a solution that optimises transcranial ultrasound propagation for blood-brain barrier opening can be an interesting development for brain applications. Benlloch and team recently patented such a device, which works by applying high-intensity focused ultrasound (HIFU) to a membrane created with a 3-D printer using CT or MR images. The difference with HIFU is that the solution only uses one ultrasound transducer.

'We mold the crane based on information from a CT or MR scan. We create the membrane, with a 3-D printer, to highlight which brain area we want to focus on with ultrasound. This could be helpful for neurostimulation,' he pointed out.

MRI is excellent to image soft tissues but not so much for hard tissue, such as teeth or bone. The MRI lab at I3M therefore developed MR technology for simultaneous visualisation of both soft and hard tissue in dental applications. 'Teeth produce a signal on MR, provided one uses a sensor that is fast and sensitive enough to capture that signal. Our solution may be even better. We change the magic angle of MR by rapidly oscillating between tissues.' The next frontier will be to image the bone, jaws and crane indifferently, and MR has already proven it could get there using special sequences.

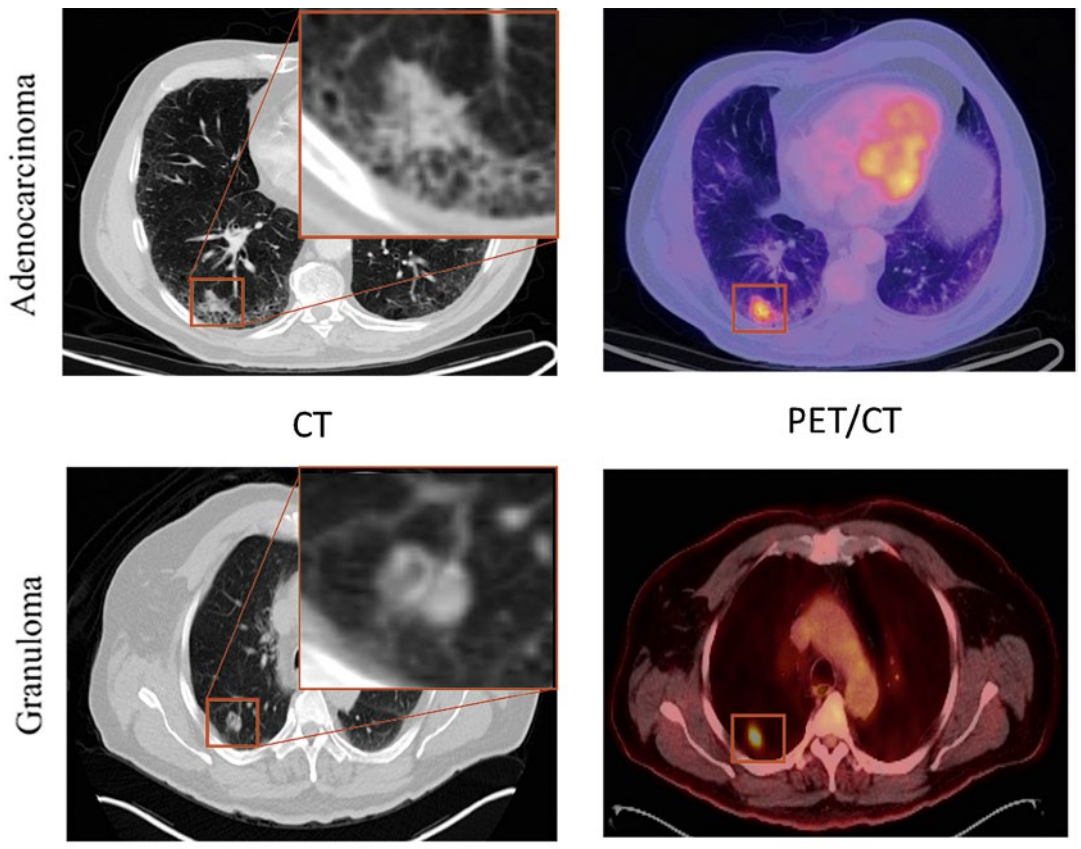
The I3M has also given birth to innovations in MR image-guided therapy, to drive magnetic nanoparticles to biological tissues using external magnetic fields and guided by MR; and vortex elasticity imaging, using acoustic vortices. The institute has also pioneered MRI development at the cellular range, with non-invasive visualisation of individual human cells in vivo (< 10 µm) and in real-time, and in vivo mouse brain imaging with 29 µm resolution at 15.2-Tesla.

Last but not least, the group is also active in software and biomarkers development.

Radiomics is unlocking a clinical challenge

A boost for thoracic radiology

A new radiomics study could help unlock one of the more challenging issues facing thoracic radiologists, Mark Nicholls reports



Radiographic Challenge: Adenocarcinomas and Granulomas are largely indistinguishable on CT and PET scans

Distinguishing non-small cell lung cancer from benign nodules is a major challenge due to their similar appearance on CT images. Now, however, researchers from Case Western Reserve University in Cleveland, Ohio, have used radiomic features extracted from CT images to differentiate between these two pathologic conditions.

Researcher Niha Beig explained that previous work on computer aided diagnosis (CAD) of lung cancer on CT, using radiomics, focused on investigating the suspicious lung nodule alone, but the retrospective study evaluated the computer-extracted (radiomic) features of the nodule in question as well as an immediate region of the lung parenchyma outside the nodule.

Cqptuing patterns on CT imaging using radiomics

It is known that tumour-infiltrating lymphocytes and tumour-associated stromal macrophages in the stroma around a tumour is associated with the likelihood of malignancy, but her study team wanted to explore the idea of potentially capturing these patterns on CT imaging, via radiomics.

The study demonstrated that a combination of radiomic patterns of heterogeneity within and outside the tumour could distinguish benign nodules from non-small cell lung cancer on CT scans with 80% accuracy. On the same test set, an accuracy of 75% was obtained when they assessed only the nodule by itself.

Beig said the main emphasis of the work is (1) a lot of informative signal is present outside the nodule, potentially capturing the malignant micro-environment of a tumour, and (2) combing the radiomic features from this region outside the suspicious nodule with the nodule itself can help build more robust CAD systems.

To reach their conclusion, the researchers developed a supervised machine learning pipeline and a dataset consisting of 290 patients (145 were benign granulomas, and the rest were malignant non-small cell lung cancer nodules).

Within the training subset of 145 cases (with equal representation of two classes), radiomic features were extracted from the nodule and the region immediate to the lung parenchyma around the nodule. Following feature selection, a support vector machine (SVM) classifier was built and validated on an independent test set the remaining 145 cases.

Attempting to unravel the morphometric and biological basis in radiomics

'Using the performance metrics of accuracy, sensitivity and specificity we concluded that radiomic features from inside the nodule and immediately outside the nodule can differentiate malignant tumours from benign nodules,' Beig said.

Another important aspect of this study was the qualitative assessment of representative patient histology in an attempt to unravel the morphometric and biological basis for the most predictive radiomic features.

'We found that the immediate vicinity of 5mm outside the tumour had a unique radiomic signature in adenocarcinomas. We hypothesise that this densely-packed stromal tumour-infiltrating lymphocytes around adenocarcinomas manifest as smooth texture on CT images and potentially results in this distinctive radiomic signature.'

Given that differentiating the two pathologic conditions of non-small cell lung cancer and benign nodules - due to their similar appearance on CT images – is recognised as one of the most challenging issues faced by thoracic radiologists, she explained the significance of these findings.

'Adenocarcinomas are the most prevalent subtype of non-small cell lung cancer, making it the most common true-positive finding in a given non-contrast lung cancer screening population. Granulomas represent the most common and possibly most confounding false-positive finding,' Beig explained.

'Given the similar appearance of these two pathologic conditions on imaging, a CAD based approach to this pressing clinical question is of immense interest.

'Our study found that CT imaging can be leveraged by using artificial intelligence algorithms to capture sub-visual textural clues of the tumour biology that can't be appreciated by the naked human eye of an expert.'

She added that findings suggest a significant wealth of malignancy-related information in the peritumoral region of the tumour, such as angiogenic activity that manifests within the peritumoral region on CT imaging.

Beig believes the findings could have an impact on future clinical practice. 'I think the very context of integrating AI in healthcare is to aid better diagnosis and personalise treatments for prolonged survival in cancer patients. Our work represents a preliminary success for better diagnosis of malignant findings in a given lung cancer screening population.

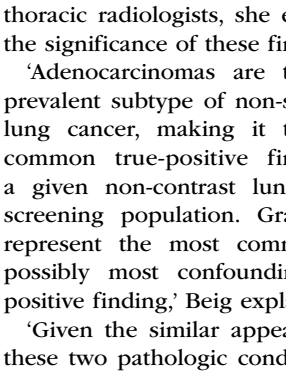
'We started with the intention of developing a CAD tool that can reduce the number of interventions and unnecessary imaging needed to confirm diagnosis. We still hope that this technology will have a positive impact on the future clinical practice, and be used for this purpose.'

When implemented in clinical practice, the technology will potentially aid clinicians/radiologists to confirm diagnosis and subsequently make informed treatment decisions for example, whether a biopsy is required or not, as well as to improve the patient management protocol.

Beyond that, patient benefits are also significant. The National Lung Screening Trial in the USA showed that 95% of incidental findings on CT are benign, and a majority represent benign granulomas, but many patients still undergo surgical intervention e.g. a biopsy, bronchoscopy or surgical wedge resection for histopathologic confirmation of presence or absence of a malignancy, or multiple CT scans for continued evaluation of the nodule.

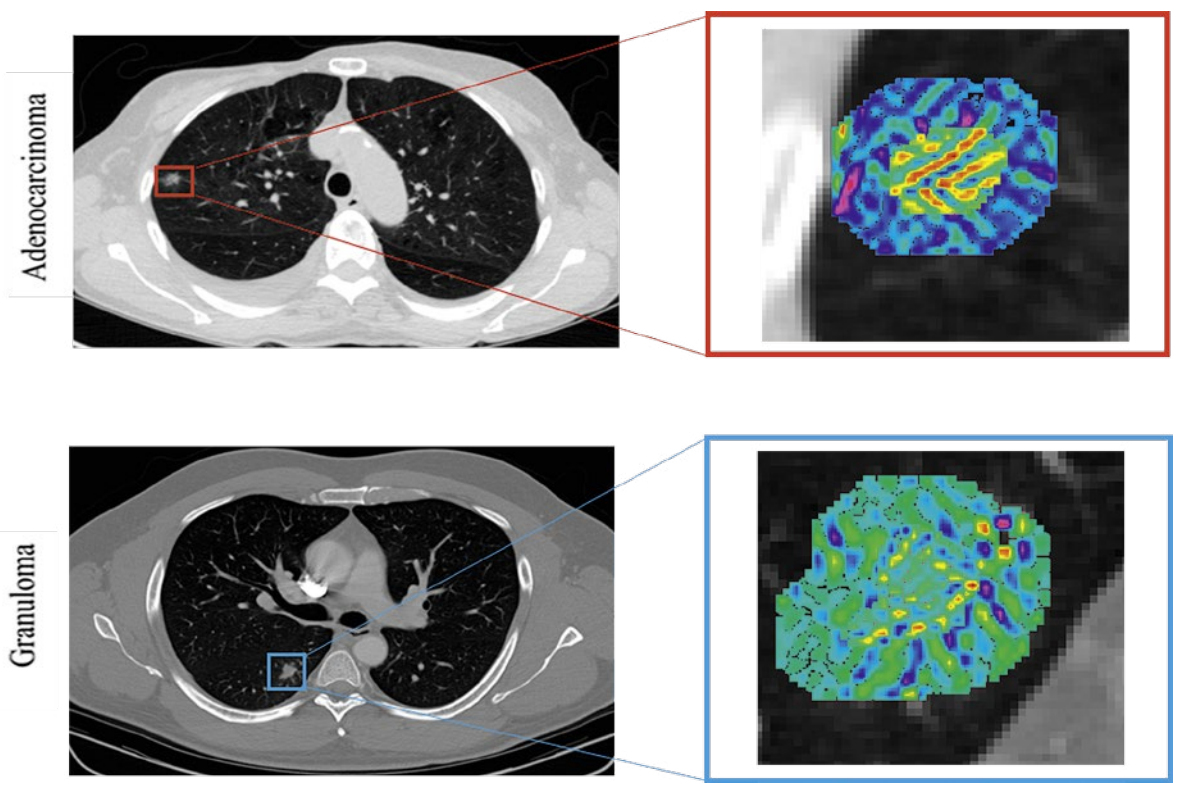
'Recognising that there is an unmet need for decision support tools for analysis, our work would be a far better tool,' Beig affirmed. 'Our technology can be translated as a simple and inexpensive diagnosis tool, compared to an existing CAT scan, to determine whether a patient needs more invasive and expensive procedures or not.'

However, she acknowledged that further work needs to be done before its realisation as a cancer screening tool to integrate into clinical practice in terms of validation, planning and more comprehensive analysis.



Professor Anant Madabhushi, director of CCIPD

Niha Beig is a third year PhD student in the biomedical engineering department at Case Western Reserve University, Cleveland Ohio, USA, where she works under the guidance of Professor Anant Madabhushi, the principal investigator and scientific guarantor of this study and director of the university's Center for Computational Imaging and Personalised Diagnostics (CCIPD), where this study was conducted.



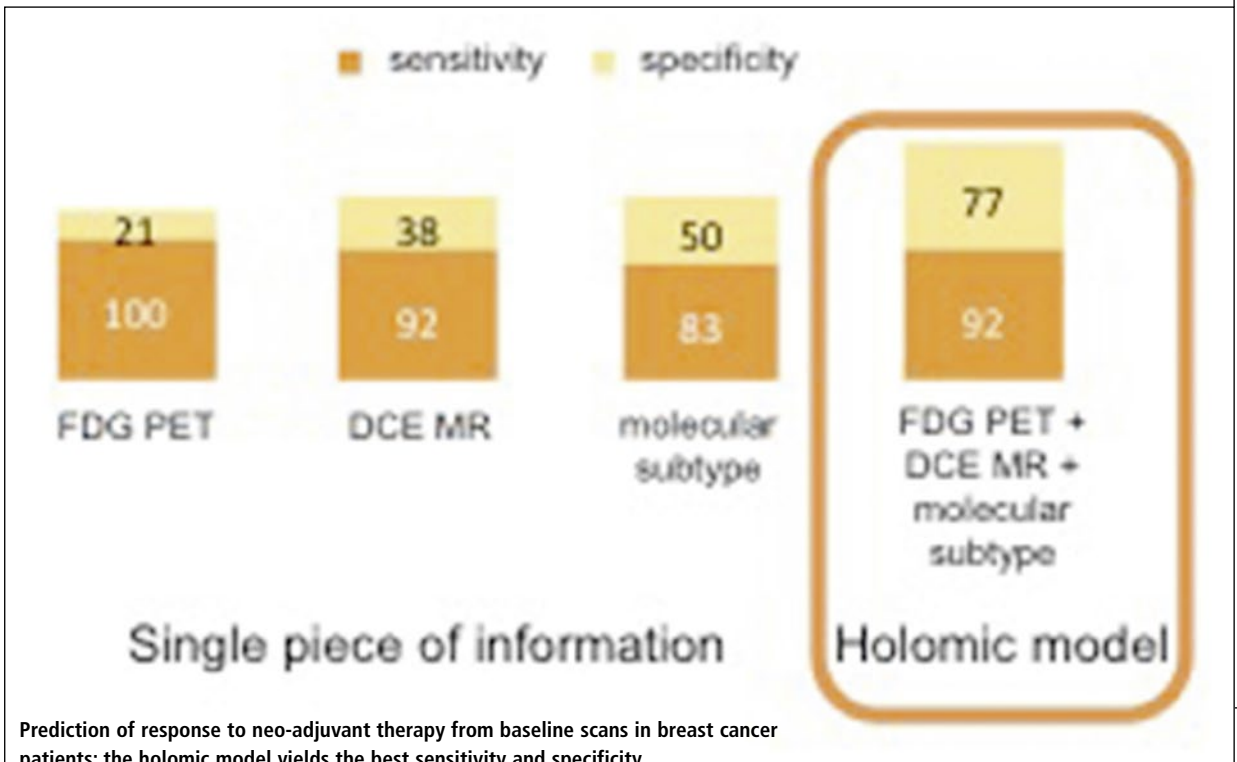
Unique radiomic signatures from intra- and peri-nodular regions on CT imaging can distinguish adenocarcinomas from granulomas

Predicting the truth from hybrid imaging

Holomics is a trendy but complex topic

'Is it possible to know whether a treatment will work before even starting it – in other words, to predict the truth? That's the great promise of holomics, a concept that everyone has been involved in without even noticing,' said leading French physicist Irène Buvat, from the In Vivo Molecular Imaging French lab, who is set to focus on this subject at ECR 2019 (Vienna. 27 February to 3 March 2019).

Exclusive interview by Mélisande Rouger



Prediction of response to neo-adjuvant therapy from baseline scans in breast cancer patients: the holomic model yields the best sensitivity and specificity

When **Irène Buvat** gained her PhD in Particle and Nuclear Physics from Paris Sud University, France, in 1992, the physicist oriented her path towards nuclear physics for medical imaging applications. After a year at University College London, UK, and two more at the National Institutes of Health, Bethesda, USA, in 1995 she joined the French Centre National de la Recherche Scientifique. Buvat now heads the In Vivo Molecular Imaging research lab at the Service Hospitalier Frédéric Joliot PET centre in Orsay, where her research focuses on developing quantification methods to make the most of SPECT and PET data coupled with CT or MRI, to understand biological mechanisms for optimising patient management. She is involved in radiomic and holomic approaches to further enhance the role of PET/CT and PET/MR in precision medicine. Ever active in training students and knowledge and software dissemination, she promotes open-access to high-standard research material.

'The truth,' said physicist Irène Buvat, discussing whether a therapy prediction could work, 'can involve several things: the patient's response to therapy, the prognosis, patient tumour molecular subtype, dementia type, the presence of a genetic mutation – usually something that's clinically or biologically relevant. We call it truth because we want to make a prediction that will prove to be 100% accurate.'

To predict the truth, one has to account for a number of variables, such as abnormalities seen in blood samples, genetic mutations, the patient's age, condition, medical history, etc. And of course, imaging data, which are very useful and currently absolutely needed for patient management. This is especially true for hybrid imaging data, Buvat pointed out.

What are holomics?

'Holomics can be defined as the gathering of genomic, radiomic, proteomic, clinical, immunohistochemical and many more data, and their integration in predictive or prognostic models. Holomics can be seen as an extension of radiomics, which is the extraction of features from many images as a foundation for predictive models. In short, holomics is radiomics enriched by other types of data.

'In contrast to current predictive models, holomics includes all these different types of information to predict the likelihood of a patient responding to therapy, developing a certain disease, and so on. The assumption is that information reflected by images will tell us more if they are put into context, i.e. if interpreted together with other non-imaging data.'

What are the potential benefits?

'Being able to predict will definitely contribute to precision medicine, because if we can predict that a patient has a very low likelihood to respond to a given chemotherapy and there is an alternative treatment, that treatment will be given first.

'Patient management also heavily depends on the experience of the specialists involved. The idea with holomics is to erase this difference by integrating different kinds of information on a quantitative and reproducible basis to assist therapeutic decisions. Any decision would of course be made under the control of a specialist, but the algorithm would always provide expert knowledge. '

Where is it interesting to use holomics?

'Holomic approaches are mainly being developed in oncological imaging, but are also valuable in cardiovascular and brain imaging. Right now, people creating scores involving image-derived parameters and other patient features like age are doing holomics without noticing. The word was first coined in the context of tumour imaging. 'Holomics is a trendy, but complex topic, he pointed out. 'We have a few results combining blood markers with imaging markers, but we could have far better results if we could add information from genomics as well as other fields.'

Why is it appealing to implement holomics with hybrid imaging?

'The more different the imaging data, the deeper we can use holomics. Hybrid imaging gives information from two imaging modalities in the same machine at the same time, which makes it a privileged gateway to collect many distinct types of information. PET and MR offer complementary but non-redundant information that can give a more complete profile of the disease. We can see anatomic characteristics on MR and, at the same time, metabolic features on PET, and additional functional features using different MR sequences.

'The main obstacle now is to collect enough reliable and rich data to build holomic models. There are fewer hybrid imaging modalities, but the information they provide is richer than CT or MR scanners alone. In hybrid scanners, images are perfectly aligned in space and time, unlike two exams performed on two different machines at different times.'

How exactly do holomics work?

'We use both shallow and deep learning, which differ in the way information is extracted from the data. To design a model, three types of learning techniques can be employed: supervised, unsupervised or reinforcement learning; supervised and unsupervised being by far the most frequent now.

'As an example for supervised learning, we tell the algorithm which tumours in a data set are benign and which are malignant. Then, the machine learning approach will find the model that makes the most accurate prediction for the data present in the training set.

'Unsupervised learning, on the other hand, is performed to try and identify trends or structures in any given data. Often, clusters can be identified, i.e. groups of data that are similar within each group and different between groups. This approach is very useful because it might reveal trends that we are completely unaware of and might give rise to new hypotheses.

'In reinforcement learning, we do not provide the algorithm with examples of images associated with the right class they belong to, but we give feedback in the form of reward or penalty. This approach mimics the way humans learn.

'Therefore, the overall current challenge is to make the most of these different approaches to integrate medical images and associated data, and produce new knowledge that will help the medical doctors to optimise patient management.'

Radiomics on tap in 5-10 years

Continued from page 9

ity of the biomarkers used in a trial. 'Radiomics signatures must meet the TRIPOD level 4 to be deemed worthy. Prospective studies may also be required, with a predetermined signature that needs to be validated in the study,' he said.

Software must also receive CE mark or FDA approval. Integration into the hospital workflow is key for the solution to bring value. Last but not least, reimbursement can be problematic when financial incentives go in the wrong direction. 'Using our radiomics signature, we can reduce the number of useless interventions in kidney cysts, for example, but in some countries hospital managers argue that they are paid per intervention,' he said.

Combining the best of DL with radiomics

An interesting path to explore in the future is the alliance of radiomics and deep learning (DL), notably to develop non-invasive imaging based biomarkers for radiomics. 'Current research combines the best of DL, in particular automated segmentation, with the best of radiomics, by enforcing robust image characteristics into DL,' Lambin pointed out. 'This looks like a promising approach.'

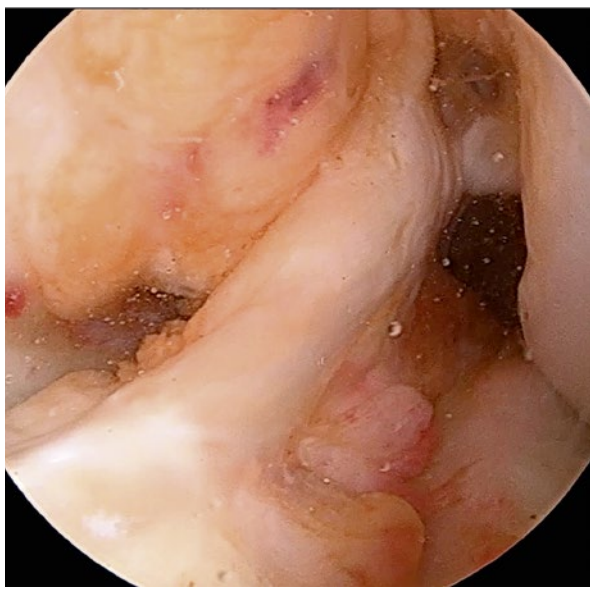
DL uses a radically different method than radiomics, in which image characteristics with an already known image signature, for instance heterogeneity, are selected. So far no one can explain how DL works exactly. 'It's a black box; we don't really know how it works , which is annoying because doctors like to understand the process,' he said.

DL also requires more horsepower to train its algorithms to distinguish between a malignant and a benign tumour. To feed the beast, DL needs at least 10,000 images and, sometimes, synthetic data. 'If we could have a million data, I bet that DL would be better than traditional radiomics. But,' he concluded, 'we would still have the issue of an uninterpretable algorithm.' (MR)

Correlations of MRI and arthroscopy

Teaching the subtleties of knee diagnostics

Five days following injury, sagittal MRI image shows mid-substance discontinuity of the anterior cruciate ligament (ACL).



Four months following injury, arthroscopic image confirms ACL rupture, showing ACL displace-ment from the lateral femoral condyle and scarring to the posterior cruciate ligament

Magnetic resonance imaging (MRI) knee exams are essential to orthopaedic surgeons to diagnose the cause of symptoms in patients with knee pain and to plan arthroscopic treatment. Yet, surgeons who treat patients based on knee MRIs, and radiologists who interpret those knee MRIs, often work in their own silos of specialisation, rarely communicating and sharing information, according to William Palmer MD, Director of Musculoskeletal Radiology & Intervention at Massachusetts General Hospital, a teaching hospital of Harvard Medical School in Boston.

MRI scans of knee compared with arthroscopic findings.

This lack of communication puts radiologists at a learning disadvantage. Although radiologists review many MRI knee studies, and report findings that include meniscal tears and cartilage defects, they may not receive feedback on the accuracy of their interpretations. A meniscus reported by a radiologist as torn may be diagnosed as normal at arthroscopy, or a meniscus that a radiologist reports as normal may be diagnosed as torn at arthroscopy. Without surgeon's feedback, or access to arthroscopy notes, radiologists work in a vacuum. They may fail to learn from their mistakes and are then more likely to repeat their diagnostic errors.

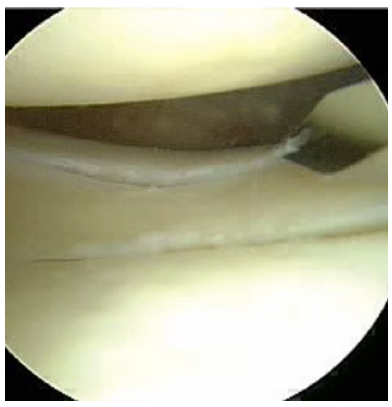
Because arthroscopy is the gold standard in the diagnosis of internal derangements of the knee, Palmer spoke on 'Knee: MRI - Arthroscopy Correlation' at the 18th MRI Symposium held recently in Garmisch. His focus was on sports-related injuries and a biomechanical approach to traumatic knee injuries, and he compared the MRI appearances of knee structures with their arthroscopic appearances.

Correlating MRI and arthroscopy for diagnosis

'This comparison can be a powerful teaching tool,' he said. By correlating MRI and arthroscopy, he hopes to teach radiologists about the diagnosis of subtle but important MRI findings, including meniscal tears, cartilage defects and ligament injuries.

Sagittal MRI image shows a peripheral medial meniscal tear. This subtle tear was missed prospective

Arthroscopic image confirms the peripheral, vertical longitudinal tear of the medial meniscus



William Palmer MD is Director of Musculoskeletal Radiology & Intervention at Massachusetts General Hospital (MGH), Boston. 1984 he gained his medical doctorate from Yale University, and obtained board certification in Internal Medicine in 1987, at the Hospital of the University of Pennsylvania, plus Radiology in 1991, at MGH. When his fellowship training in MRI ended at MGH, he joined the hospital's radiology staff, where he became Director of MRI in 1995. Clinical expertise includes sports imaging, arthritis and spine intervention. Currently he oversees nine MSK radiologists and 5-7 fellows.

Algorithms will help in detecting invasive cancers and risk stratification

AI is proving pivotal in women's health solutions

Daniela Zimmermann met with Pete Valenti, Hologic's division president of breast and skeletal health solutions, to discuss how artificial intelligence is driving innovation in breast health technology.

Artificial Intelligence (AI) is proving pivotal as Hologic evolves its women's health solutions.

With a focus on breast and skeletal health, future steps will see the medical technology company incorporate a more integrated approach to drive better, more cost effective, outcomes that are clinically supported to deliver an improved patient experience.

Underpinning that evolution more recently has been the acquisition of two organisations – digital specimen radiography specialists Faxitron Bioptics and BioZorb marker manufacturer Focal Therapeutics – as Hologic drives harder into the breast surgery side of that continuum.

Speaking to European Hospital, Pete Valenti, Hologic's division president of breast and skeletal health solutions, explained: "One of the things that has always differentiated us - besides having superior clinical outcome data - is our ability to integrate."

From integrating biopsy into mammography to lead to lower costs and better outcomes, he indicates that the same direction will occur with surgery.

With Artificial Intelligence becoming increasingly important in healthcare, he points to it as being a key component in Hologic's success in achieving higher rates of invasive cancer detection, coupled with lower rates of recall.

"We have been doing Artificial Intelligence in our designs for years, we have an enormous database of breast cancers, and are constantly building on that database."

That, he suggests, makes finding cancer easier and faster for radiologists, and in particular via adding AI capability to tomosynthesis as a technique.

"We are the only company that has a dense breast claim because when we designed our approach we thought about the future. That future is more risk stratified, or personalised medicine, and in that world density is a risk factor," said Valenti.

"Density makes it harder to see cancers, so by design how you find those things is again with AI. When you think about how AI fits with us, it fits along that spectrum and integrated design and Artificial Intelligence are that spectrum."

AI can also perform the basics such as helping technicians do their job more efficiently, which ultimately sits within the cost equation alongside better patient experience and faster procedures within the workflow space.

Valenti highlights Hologic's Brevera® breast biopsy system with CorLumina® imaging technology in improving workflow on the biopsy side, as well as the patient experience and reducing retake and recall rates.

"Retake rates and recall rates are enemies of faster workflow," he added.

A major change he sees in the patient landscape over the next five years is the greater prevalence of available information and patients having more access to data about which providers deliver better detection and outcomes and which offer best value.

He sees Hologic benchmarking that data via an analytics platform that is more predictive and will show outcomes and details such as comparisons in retake rates and which provider is best at reducing that.

Again, AI plays the pivotal role across the entire spectrum, he said, with algorithms and deep learning and the ability to learn and process on a continuous basis.

"To do that we have to feed in the data – more cancers, more false positives – and that allows AI to determine differences between a positive and a false positive, so we are constantly adding much more data into the engine."

He sees an environment where AI will handle straightforward cases, leaving the radiologist to focus on more complex and unclear cases and also potentially eradicating the role of mandatory second reads in Europe, a move he suggests will lead to significant costs savings.

"The more complex cases are going to need more radiologist attention but if a patient does not have to come back because they do not have the cancer then that improves the patient experience."

The screening environment, he predicts, could shift with "risk stratification" – the watchwords.

"The work we are doing with key partners on risk stratification and patient pathway is that the baseline should be much younger and that some patients should go (for mammography) every four years, some every six years, and others every six months depending on their risk profile and history.

"Risk stratification is the world we are going to live in and that is an exciting world. By getting rid of some of pain associated with mammography, some (women) will want to go more because the experience is better."

He said Hologic, and its key partners, want to drive this process using data and clinical support.

One area Hologic is working on with a partner is a genomic testing model with mammography that can predict the cancer recurrence rate.

If the model suggested that the recurrence rate with high probability was not going to be for 5-10 years then a patient would not need to come back so soon. Yet if it suggested a recurrence in two years, then a sooner re-examination could take place in order to pick up any possible recurrence at the earliest opportunity and improve survival rate.

"That world is the world that is coming," he continued, "and AI used in the patient pathway means we can 'customise' the journey with higher confidence."

However, he stressed the importance of having a high number of cases to create the AI capability and revealed Hologic has plans to extend

Future magnetic resonance scanners

MRI speed and versatility raised by AI

'MRI in five minutes – Dream or Reality?' That's the question posed and answered by Dr Daniel Sodickson during the International MRI Symposium held recently in Garmisch-Partenkirchen, Germany (17-19 January).

Sodickson, from the New York University School of Medicine, sees a number of changes entering imaging, including artificial intelligence (AI), which will make MR imaging much faster and more versatile. 'I see the five-minute MRI as a sort of bellwether for trends in imaging today,' Sodickson said. 'AI might enable a new parable of ultra-fast MRI that's going to change the experience of the patient and day-to-day workflow of the radiologist. There will be a number of other changes that go along with AI to make imaging super-fast.'

An alternative title for his talk might have been: Imaging in a changing world: the scanners of the future and the future of scanning. 'In the future,' he predicted, 'MR scanners will move from snapshots to streaming.'

AI as the brain of MRI

Traditionally, clinicians devote their efforts to one view of the anatomy, or a series of slices, or dynamic view, pausing between shots to carry out the examination setup. In the future, Sodickson predicts that software will adapt to a more modern paradigm, in which the scanner gathers information about the patient continuously and the software then pieces the images together.

A flexible MRI detector array in the form of a glove. Top: photos of the hand in various poses. Bottom: corresponding MR images obtained using the glove. With multifaceted sensor technology like this, MRI can embrace new flexibility.

(Credits: Bei Zhang, Martijn Cloos, Daniel Sodickson. Zhang B et al, Nature Biomedical Engineering 2018;2(8):570-577. A high-impedance detector-array glove for magnetic resonance imaging of the hand.)

Sodickson likens this to a 'move from emulating the eye to imitating the brain', and asks, 'How do we make sense of all that information? The model can come from how our own brains work.'

All our senses — hearing, sight, smell, touch — are filtered through the brain, which turns them into actionable information. Similarly, AI can take the information from continuously acquired datasets and can then reconstruct full images from partial data.

Snapshots are dead, long live streaming

As part of his work, Sodickson and the NYU School of Medicine's department of radiology is collaborating with the Facebook Artificial Intelligence Research (FAIR) group to speed up MRI scans while still acquiring enough data.

He sees the work developing in two phases — using existing technology to gather less data and then innovating scanners to operate differently, almost like a self-driving car with multiple sensors.

'The days of the carefully framed snapshot are, if not already over, certainly limited,' Sodickson said. 'It behoves everyone to think about how to construct data streams rather than image series. In MRI, and imaging more broadly, we're not just following our eyes anymore; we're emulating how we see the world. Stay tuned for imaging devices that start looking and feeling radically different than we're used to.'

The Facebook AI research cooperation

At the end of November 2018, the NYU School of Medicine's Department of Radiology released the first large-scale MRI dataset of its kind as part of the fastMRI project launched earlier that year with Facebook Artificial Intelligence Research. While other sets of radiological images have been released previously, this dataset represents the largest public release of raw MRI data to date.

The first phase of the project will involve data from knee MRI scans, but future releases will include data from liver and brain scans. 'This collaboration focuses on applying the strengths of machine learning to reconstruct high-value images in new ways.

'Rather than using existing images to train AI algorithms, we will radically change the way medical images are acquired in the first place,' Sodickson explained.

'Our aim is not merely enhanced data mining with artificial intelligence, but rather to create new capabilities for medical visualisation, to benefit human health.'

Dr Daniel Sodickson is professor and vice chair for research in the radiology department at NYU, and a principal investigator at the Center for Advanced Imaging Innovation and Research. He also a director at the Bernard & Irene Schwartz Center for Biomedical Imaging. Having gained a BSc in Physics and BA in Humanities from Yale College, he received his PhD in Medical Physics from MIT and MD from Harvard Medical School, both as a part of the Harvard-MIT Division of Health Sciences and Technology. Sodickson's research primarily focuses on developing new techniques for biomedical imaging, with the broad aim of seeing what has previously been invisible. He is credited with founding the field of parallel imaging, in which distributed arrays of detectors are used to gather magnetic resonance images at hitherto inaccessible speeds.

Source: Hologic

Pete Valenti is Hologic's division president of breast and skeletal health solutions

the concept from AI mammography to the world of ultrasound – working in partnership with Clarius - whilst continuing to expand its expertise within the breast diagnosis and therapeutics field.

In terms of tomosynthesis and 3D mammography, he said Hologic is driving innovation faster than any other organisation and that is primarily because of the clear focus on breast care.

As for the future, he said an area of development is increased portability and also looking to integrate processes as well as the ability for health systems to better access patients away from a hospital setting.

The aim, concluded Valenti, is to deliver improved outcomes and workflow as well as increase patient satisfaction as Hologic drives innovation in breast health technology.

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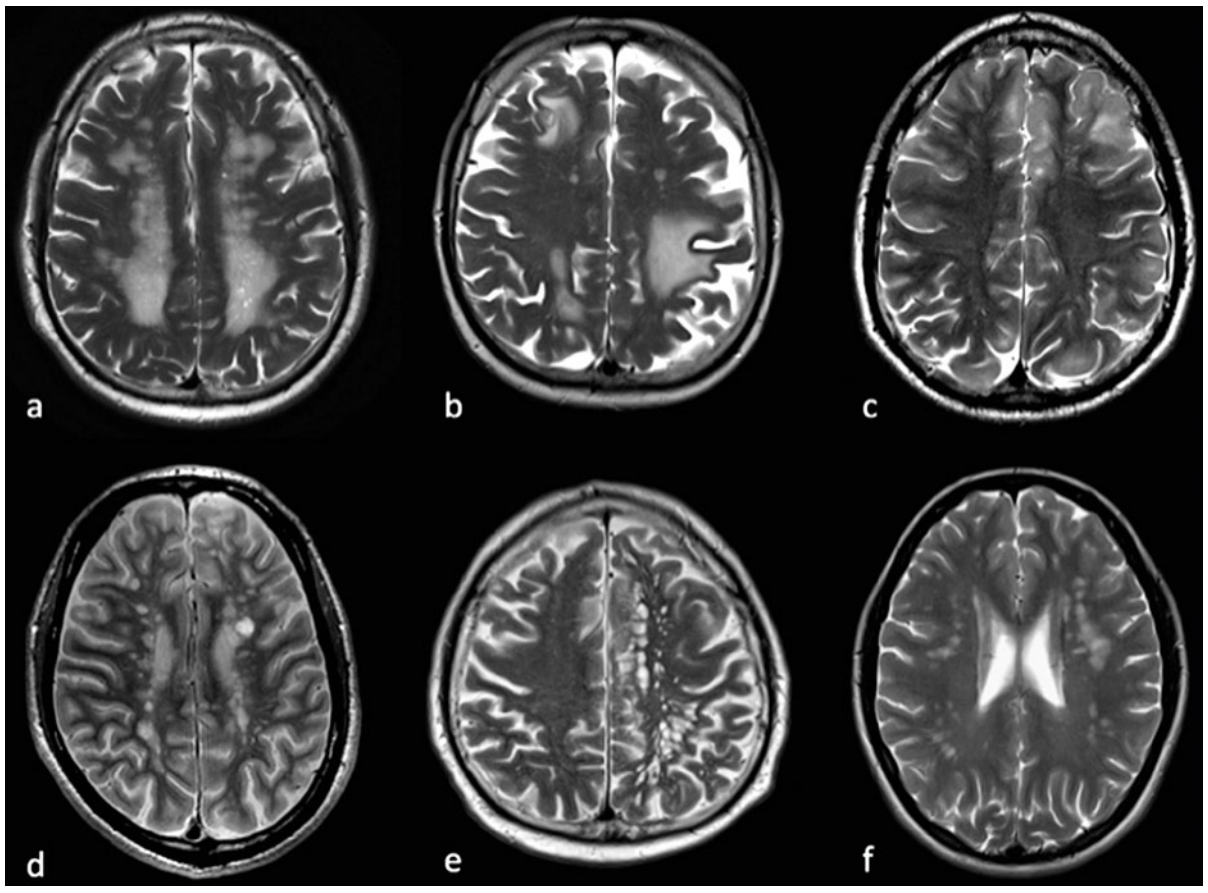
T-2-weighted images have increasing importance

When the brain turns white

White matter on the brain is a difficult subject. Even the terminology is varied, making differential diagnosis complex. An understanding of prevalence and of the tools available to facilitate the diagnosis of individual diseases is important, Dr Gunther Fesl, radiologist at Praxis Radiologie Augsburg, explains.



a: confluent microangiopathic lesions (Fazekas 3); b: metastases; c: tuberous sclerosis; d: multiple sclerosis; e: enlarged perivascular spaces (Virchow-Robin spaces); f: CADASIL

'Differential diagnosis of white matter on the brain is difficult. Even the terminology varies considerably. We talk about Leukoaraiosis, Leukoencephalopathy, white matter lesions, white matter hyperintensities, white matter changes or white matter disease,' Gunther Fesl explains.

However, as the underlying causes differ significantly, the radiologist's differential diagnosis must be accordingly precise.

'Based on a T-2-weighted image alone, it's usually impossible to make a precise diagnosis, as seen in the example image.

'The list of differential diagnoses is long. 'The reasons for white matter range from the normal, human aging process to very rare diseases,' Fesl explains. The older we become, the more of these white spots can be seen on the brain. 'The transitions from normal aging to disease are smooth,' he adds. Therefore, it is important to determine the margins to actual disease.

'Leaving aside physiological processes, such as aging, caps, bands or perivascular spaces, which are often diagnosed by chance, there can be hypoxic-ischaemic or inflammatory/autoimmune processes, right down to toxic, infectious or even traumatic occurrences in the brain. Tumours or metastases also need to be ruled out,' he points out.

The Fazekas score really helps to classify micro-angiopathies

'Whilst some confluent white matter often can be still attributed to the aging process of people in their mid-sixties, a completely confluent image is likely to be pathological.'

The Fazekas score really helps to classify microangiopathies. 'Microangiopathies correlate with dementia, depression, strokes and even death,' he explains. 'This means that the relative risk of suffering one of these events rises with the increase in white matter on the brain. However, all these manifestations are subject to smooth transitions.'

The causes of typical microangiopathies must be clearly defined: 'Along with the aging process, smoking, high blood pressure, diabetes mellitus and some other vascular factors can also be causes,' Gunther Fesl adds.

By looking at the prevalence of diseases, some can often be ruled out based on their prevalence rate. Reassuringly, hereditary diseases are classed as very rare, and even the frequently cited neuroborreliosis only occurs with a probability of 1:100,000.

'In most cases, the radiologist deals with hypoxic-ischaemic diseases requiring investigation. With a prevalence of 100:100,000, multiple sclerosis is the most common of the inflammatory diseases,' Fesl says. All other diseases are a lot rarer, but must still be ruled out.

CT images to detect or exclude bleeds and calcifications are also important

'T-2-weighted images are becoming ever more important in helping radiologists to make differential diagnoses because they can be used to detect microbleeds.

Contrast enhanced images also help to detect tumours, metastases and patterns of inflammation. For diseases such as multiple sclerosis, MRI examinations of the spinal cord and MRI scans of the head are central tools for differential diagnosis, Fesl clarifies.

CT images to detect or exclude bleeds and calcifications are also important to make a thorough diagnosis.

'Radiologists are nothing without relevant clinical information. A 30-year-old patient, for instance, is very unlikely to be suffering from microangiopathy.

'Communication with the referring physicians is therefore very important. We depend on the anamnesis, on the results of clinical examinations and readings from blood and cerebrospinal fluid to make a precise diagnosis,' Fesl says, underlining the significance of this information.

'I am convinced that, in the future, tools such as artificial intelligence and big data will really help to make differential diagnosis easier and faster.

'The recognition of patterns, which is exactly what the radiologist can achieve with his own eyes within the constraints of the time he has available on a daily basis, will be much easier with tools that can be utilised as the basis of diagnosis,' Fesl predicts.

Still, however, nothing works without communication with those who refer patients and without comprehensive background information about these patients. 'Tools,' he points out, 'can only supplement, never replace.'

Neuroradiologist **Dr Gunther Fesl** has been a radiologist in private practice at Praxis Radiologie Augsburg Friedberg ÜBAG and at the Private Practice for Radiology H15 since 2015. His scientific focus is on functional magnetic resonance tomography (fMRT), brain anatomy, interventional stroke therapy as well as further modern neuro-interventional therapies. Fesl was previously senior consultant at the Department for Neuroradiology at Munich University Hospital and head of the interventional neuroradiology division.

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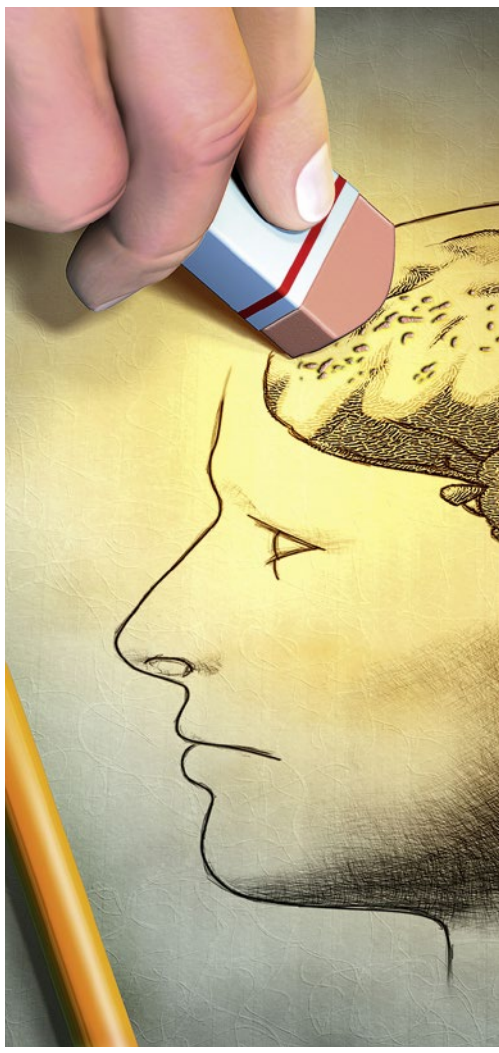


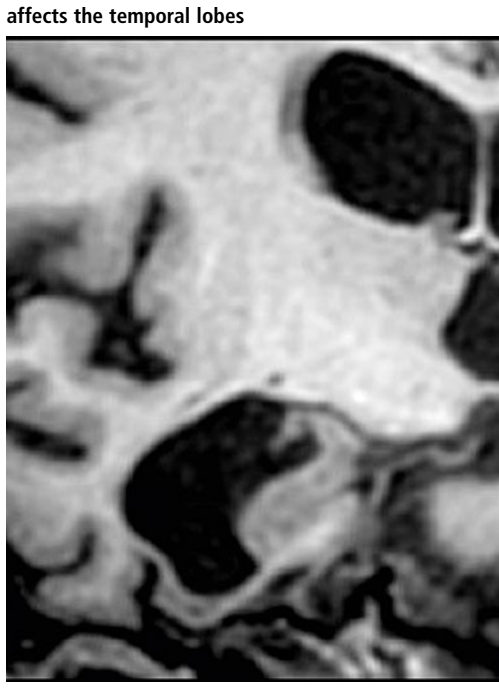
Brain imaging in patients with cognitive complaints need to be viewed differently when using MRI to diagnose and treat patients with dementia, says Dr Christopher Hess, when discussing the role of MRI in the adjunctive diagnosis of dementia at the 18th Garmisch Symposium this January.

General radiologists don't always recognise findings related to dementia

Additionally, general radiologists need to recognise important findings related to dementia when making a diagnosis.

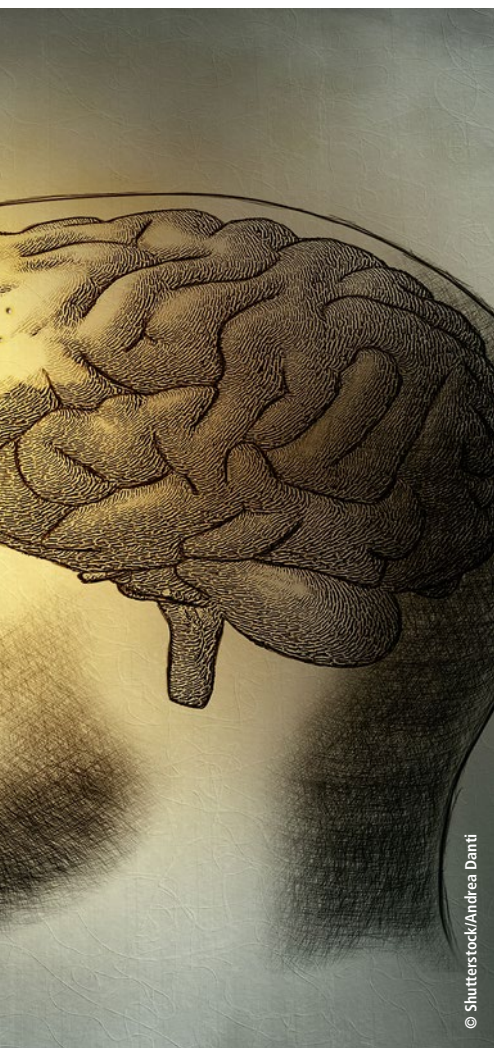
While MRI is mainly called for in patients with suspected dementia, to exclude other abnormalities, there are dementia characteristics that clinicians can look for when reading the examinations, such as specific patterns of regional brain atrophy or structural lesions in

The patient suffers semantic dementia, a variant of frontotemporal lobar degeneration which predominantly affects the temporal lobes



MRI is the first step

ntia diagnosis


© Shutterstock/Andrea Danti

areas of the brain that alter cognition, Hess pointed out.

He then discussed how radiologists can use these findings to support or refute the diagnosis of specific neurodegenerative processes, as well to recommend appropriate next steps in disease evaluation and management. He shared the approach he takes with other clinicians.

'Brain MRI,' he said, 'is often the first step in evaluation. General radiologists don't necessarily recognise the important findings related to dementia.

'We will review dementia symptoms and how they should guide the eyes of radiologists, and we'll look carefully at the critical importance of distinguishing between rapidly progressive and chronic dementia.'

Hearing how MRI, or other imaging, is used in dementia cases around the world

While MRI is the standard of care in the United States in the initial presentation of patients with cognitive complaints, that's not necessarily the case in other countries, Hess said. Some countries use CT, or no imaging at all, to examine such patients, so he found it interesting to hear discussions from delegates on how MRI, and imaging in general, is used for dementia cases in other parts of the world.

Hess believes that radiologists can play a significant role in diagnosing dementia and that MRI exams of people with cognitive complaints should be reviewed differently from patients showing with other issues.

'In particular,' he emphasised, 'it requires a sound understanding of the neuropathology and neuroanatomy of dementia.'


© University of California, San Francisco)

Dr Christopher Hess is the Alexander R. Margulis Professor and Chairman of the Department of Radiology and Biomedical Imaging at the University of California, San Francisco. He gained his PhD in Electrical Engineering from the University of Illinois at Urbana Champaign. Clinical residency and fellowship followed at UCSF. He is co-Deputy Editor of Neuroradiology for Radiology; on the American Journal of Neuroradiology, editorial board and a member of the Radiological Society of North America, the International Society for MR in Medicine, the American Society of Neuroradiology, and Academy of Radiology Research, and he is a fellow of the American Inst. for Medical and Biological Engineering, Research focus: brain degeneration, epilepsy, and neurovascular disease.

Obtaining maps that show many more structural details

7-Tesla MR enters clinical routine

Ultra-high-field magnetic resonance tomography with field strength of seven-Tesla is slowly but surely entering clinical routine. 'Thanks to very high spatial and spectral resolution, ultra-high-field MR permits detailed views of the human anatomy and can show precisely the metabolic processes such as those in the brain,' emphasised Professor Siegfried Trattnig, head of the Excellence Centre for High-Field MR at Vienna's Medical University.

The most important application is neurological illnesses such as epilepsy or multiple sclerosis. Due to the combination of better signal-noise ratios, stronger tissue contrast and higher spatial resolution, things can be seen with 7-Tesla (7-T) that cannot be seen with 3-Tesla (3-T).

Hence many patients in whom lesional focal epilepsy is suspected exhibit inconspicuous findings under 3-T, despite a firm epilepsy protocol. 23 percent of the focal cortical dysplasias — the focal disturbances in the development of the cerebral cortex, often combined with epilepsy — identified using 7-T MR cannot be detected using 3-T-MR. 'Today the suspicion of lesional focal epilepsy demands a 7-T MR — because, in the case of epilepsy, every lesion counts,' Trattnig emphasised.

Professor of Radiology **Siegfried Trattnig** specialises in high-field magnetic resonance use at Vienna's Medical University. In 2000 he became medical director of the high-field MR research scanner and, since its establishment in 2003, of the high-field MR Centre (HFMRC) of MedUni Vienna. A member of more than 50 committees in international radiology, orthopaedic and MR societies, he has over 480 technical articles to his name.

With temporal lobe epilepsy, the most common epilepsy syndrome among adults, the neuron loss in the relevant sub-regions can be made visible, a pathological classification performed and even a prognosis of post-operative outcome made.

MRT for multiple sclerosis

MR examinations with 7-T can also better visualise the plaque in grey brain matter that correlates to clinical diagnosis in cases of multiple sclerosis (MS). Furthermore there are cortical MS lesions that can be seen under 7-T but not under 3-T. 'That's why it's so important to correlate these cortical lesions with the clinical symptoms and the progression,' the professor explained. Beyond that, they are extremely helpful for differential diagnosis: it is uncommon to find cortical lesions in certain illnesses that are easily confused with MS ('MS mimics') — such as neuromyelitis optica.

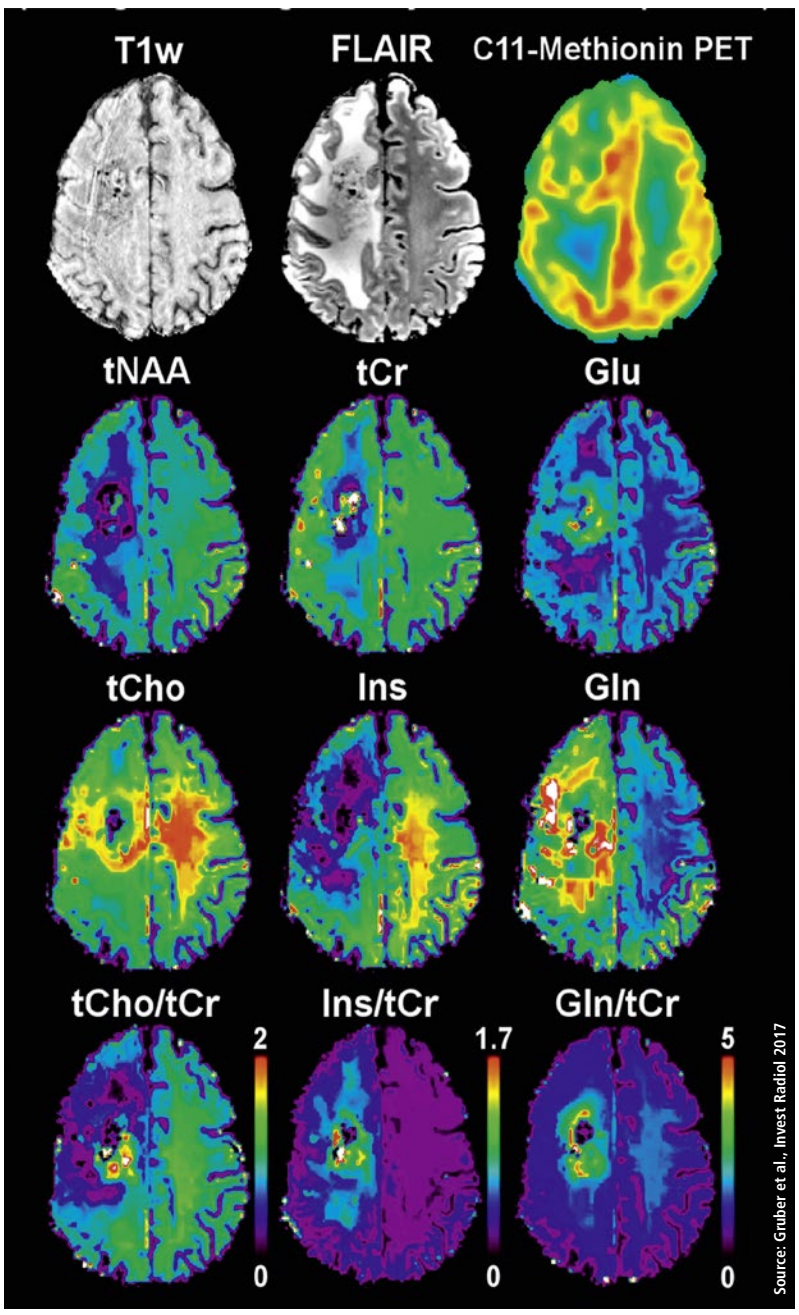
Around 40 percent of MS patients have brain lesions surrounded by iron rings. These are ferrous macrophage seams that surround some inflammation centres. However, only a third of these iron rings, visible with 7-T, can also be detected using 3-T. In Vienna it has been shown that the MS plaques that have an iron ring are slow-growing lesions, signalling progressive MS. 'The 7-T MR examination offers a chance to evaluate the effectiveness of newly developed medications against chronic progressive MS using imaging,' Trattnig pointed out. In this case the susceptibility weighted imaging (SWI) with 7-T is used.

Metabolic imaging

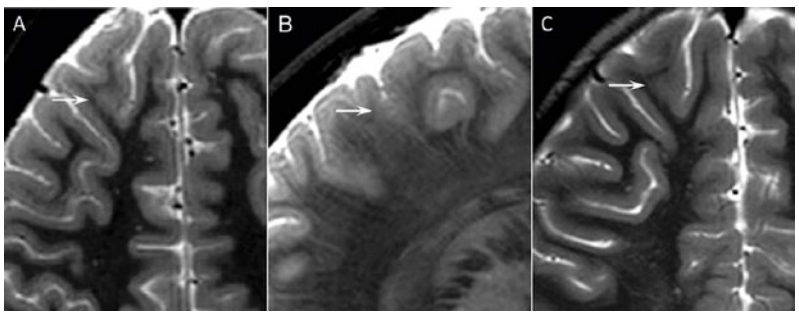
Ultra-high-field MR also permits pretty detailed metabolic imaging. 'With a resolution less that one millimetre, we already see anatomical information in the metabolic maps,' Trattnig said. Using so-called Patch-based Super-Resolution, the metabolic activity even inside small tumours can be rendered visible, such as with brain tumours that lie on the boundary between the cortex and core. Post-operative examination can render a good image of metabolic activities as an indicator of relapsing tumours around the resection zone, especially choline, a marker for tumour cell proliferation, as well as glutamine, which serves as a significant energy metabolite in some types of cancer. 'Here we have a good correlation with PET maps,' Trattnig said, 'but the 7-T MR maps show many more structural details.'

Among other things, this is of clinical significance since, in the past years, it has been found that glutamine is an essential precursor for the metabolism of cancer cells. Using 7-T FID-MRSI (FID=free induction decay, MRSI= magnetic resonance spectroscopic imaging) it is possible to distinguish the amino acid glutamine from chemically similar glutamate—the most important neurotransmitter in the central nervous system — thanks to the higher spectral resolution of the corresponding maps. 'Under 7-T, seven of the new metabolites in the central nervous system can be reliably mapped over the entire layer, under 3-T only three can be,' Trattnig explained.

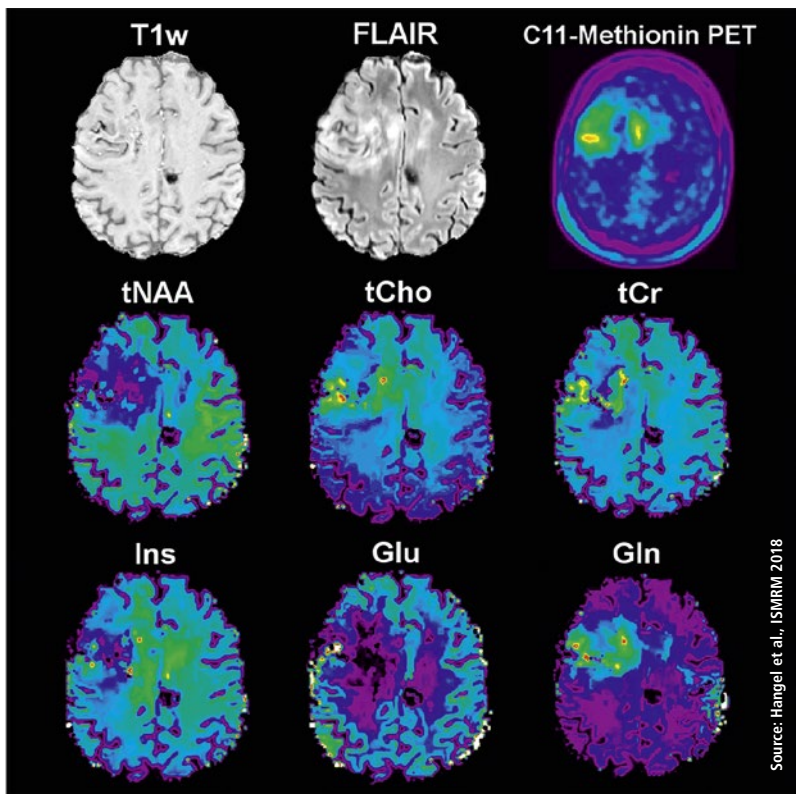
One reason the maps, generated using FID-MRSI, are better is because they enable, among other things, a more exact tumour grading and theresfore a better targeted biopsy.



At 7-Tesla 7/9 metabolites were reliably mapped over the whole slice but only three at 3-T. FID-MRSI à better metabolic maps in ~ 6 min at 7-T compared to ~ 30 min at 3-T. Improvement at 7-T in tumour grading; tumour extension definition; detection of recurrence; improved biopsy guidance.



In epilepsy every lesion counts! Detection of Focal Epilepsy at 7-T. Patients à 7-T MRI if lesional focal epilepsy is suspected, but no abnormalities at lower-field MRI scans with a dedicated protocol. 7-T MRI identified focal cortical dysplasia and mild cortical malformation in 23% that were not seen on lower-field MRI (9/40) à guiding in surgical planning.



Patch-based Super-Resolution of 7-T MRSI of Glioma. Suspected recurrence after the resection of a WHO grade II oligodendroglioma. Metabolic activities around the resection zone, especially for Cho, a marker linked to tumour cell proliferation, and for Gln increased in cancer cells even in non-CE areas. These results correspond to the PET map à more structural detail.

Multidisciplinary care is key to cardiac disease management

Research with 7-Tesla MRI

New 7-T MR methods could potentially shed light on cardiomyopathies' principles, according to a leading French radiologist who also stresses the importance of teamwork between radiologists, cardiologists, surgeons and anaesthesiologists.

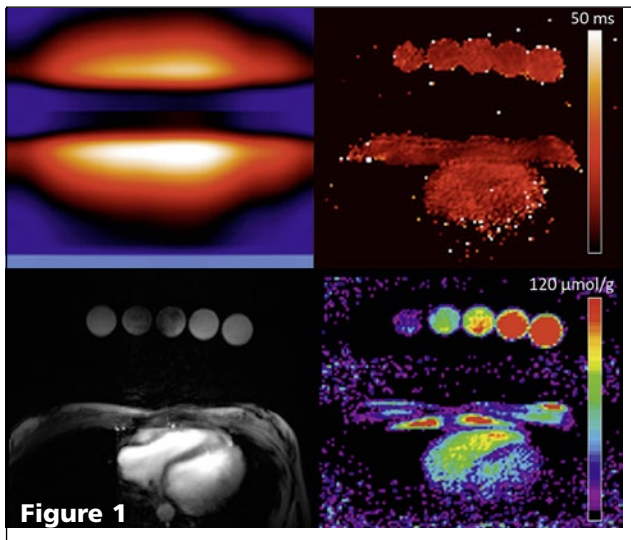


Figure 1

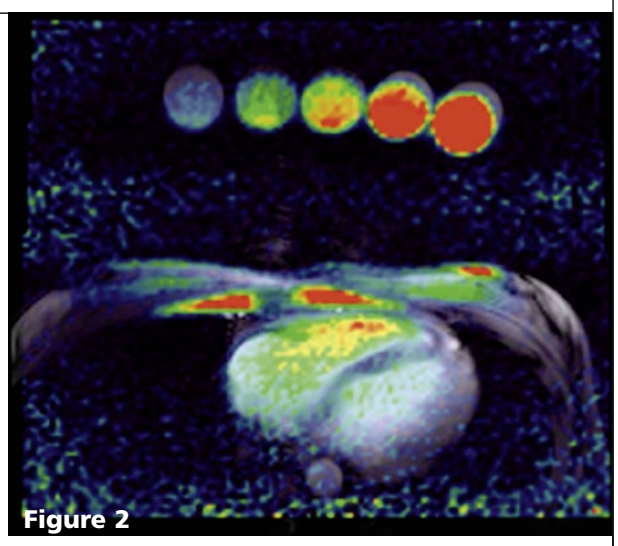


Figure 2

Sodium mapping of the heart using 7-Tesla MRI

Higher signal-to-noise ratio (SNR) using 7-Tesla MRI allows to map sodium in the human heart. The isolation of the long relaxation sodium component (using a long echo time) and the compensation of concomitant signal modulation (T2star and B1+/B1- from transmit-receive coil) allows for a single slice to be mapped within 5min at a resolution of 2x2x10 mm³. Reference sodium concentration vials attached to the coil serve as calibration of the sodium MRI signal.

Figure 1: Top-left is B1+/B1- map, Top-right is T2star map, Bottom-left is anatomical MRI image of the heart using conventional 1H-MRI, and bottom-left is the map of long-relaxation sodium concentration after corrections of the sodium MRI signal using the maps at the top.

Figure 2: Overlay of long-relaxation sodium map onto the anatomical MRI.

Morphologic and dynamic information of the myocardium is achieved with millimetric resolution (0.9x0.9 mm²). Strong intensity variations characteristic of 7-Tesla MRI can be observed from anterior to posterior myocardial segments.

New tools provided by industrial partners and used by cardiovascular surgeons and radiologists are improving treatment of thoracic aorta pathologies.

An increasingly used technique is fusion imaging, in which pre-treatment MR and CT scans of the patient are being fused with angiography images to guide stent-graft navigation through the vascular structures of the patient during the intervention, according to Alexis Jacquier, cardiovascular radiologist at Timone University Hospital in Marseille.

'Fusion imaging enables to lower radiation dose and to reduce the amount of contrast media that are traditionally required in this type of surgery. It avoids having to inject iodine to know where we're at,' he explained.

Covering full aortic pathology management, from diagnosis to care and follow-up

The hospital also hosts the Timone Aortic Centre (CAT in French), a leading regional multidisciplinary centre that covers full aortic pathology management, from diagnosis to patient care and follow-up, with a strong connection with the university. The CAT includes vascular and cardiac surgeons, radiologists, cardiologists, vascular physicians and anaesthesiologists.

The objective is to provide a multidisciplinary approach to provide the best medical care; for instance all thoracic stent-graft procedures are performed by a multidisciplinary team comprised of vascular surgeons, radiologists and anaesthesiologists at CAT.

Imaging has become key in thoracic aorta treatment with the boom of minimally invasive procedures. Besides thoracic disease, Timone Hospital is one of the main centres in France offering endovascular interventional radiology skills to treat patients with carotid and renal disease, which Jacquier and colleague Vincent Vidal perform daily, along with the full suite of cardiovascular interventional radiology procedures – endoprostheses and stent placement, small vessels and tumour embolisation, etc.

Furthermore, the hospital is located close to the medical and biology MR centre (CRMBM), one of the few laboratories in Europe that work with 7-T MRI for diagnostic imaging research.

This proximity enables Jacquier and team to test 7-T methods using sodium instead of proton imaging, a possibility that opens brand new perspectives in heart imaging. 'Sodium electrolytic disorganisation in the myocardium can have an electrical and mechanical impact on heart function.

7-T will enable the development of new applications in the field. It is still a complex task, but we are working hard on different papers on sodium quantification in the myocardium and potential clinical applications' he explained.

Cooperation with cardiologists is essential in myocardial disease management, according to Jacquier, who again stressed the importance of the multidisciplinary approach during patient treatment. 'Patients are now being cared for within the heart team, a model increasingly followed by healthcare facilities in France and beyond,' he explained.

'Whether it's for TAVI procedure, diagnosis or follow-up. Medicine is becoming hyper specialised and mixing profiles and specialties enables us to significantly improve patient care.'

Obligatory three-step training for residents in emergency radiology

Another significant development in France was the reform of the radiology residents' training scheme, which was introduced in 2017. Radiology residents must now undergo a three-step training, including successively: base training (one year), dedicated to emergency radiology; in-depth training (three years), to ensure that every subspecialty in radiology has been covered in their education; and consolidation training (one or two years), providing certification for one or two subspecialties.

Cardiovascular radiologist **Professor Alexis Jacquier**, at Timone University Hospital, Marseille, France, trained in Marseille and Lyon and gained his PhD in San Francisco, USA, supervised by Maythem Saeed and Charles Higgins. In 2006 he integrated the cardiovascular group in the CEMEREM research lab (http://crmbm.univ-amu.fr). He is author and co-author of more than 90 peer-reviewed publications and has presented numerous lectures, tutorials and refresher courses internationally. He also chaired the European Society of Cardiac Radiology membership committee and is current vice president of the French Society of Cardio-Vascular Radiology (Société Française d'Imagerie CardioVasculaire, SFICV).

prescribes the CT and MR scans and radiologist performs the technical assessment and writes the report – and then sends it to the cardiologist. Jacquier: 'This division of tasks promotes the best possible medical care, but everything really depends on the physician's skills. A lot of things may need to be updated as we gradually introduce artificial intelligence.'

Radiologists must also homogenise the way they write the imaging report. Introducing the structured report to exploit data at national level will prove essential for their future.

Another priority is to improve communication not only with patients but also other medical specialties, he said.

The French Council of the Teachers of Radiology (CERF) has been piloting the change for radiology. The French Society of Cardiovascular Radiology now provides e-learning material to ensure homogeneous teaching and training program across the country.

Last September, the series became freely available for French residents on the CERF website, and also available for all radiologists on the website of the French Society of Radiology.

This change is a substantial improvement in the training scheme, because it reflects daily routine better, Jacquier added. 'Cardiac imaging studies are being prescribed every day by all sorts of physicians: GPs, endocrinologists, surgeons, and even oncologists, for instance in pre- and post-chemotherapy evaluation.'

Many things may need updatewing for AI

As for cardiology, the French Society of Cardiology and the French Society of Radiology established a working protocol in 2005; according to this, the cardiologist

The radiologist is no longer alone in a basement reading scans,with no contact

Jacquier will participate in the International Day of Radiology (8 November 2018), an initiative to highlight the radiologist's role in cardiac care.

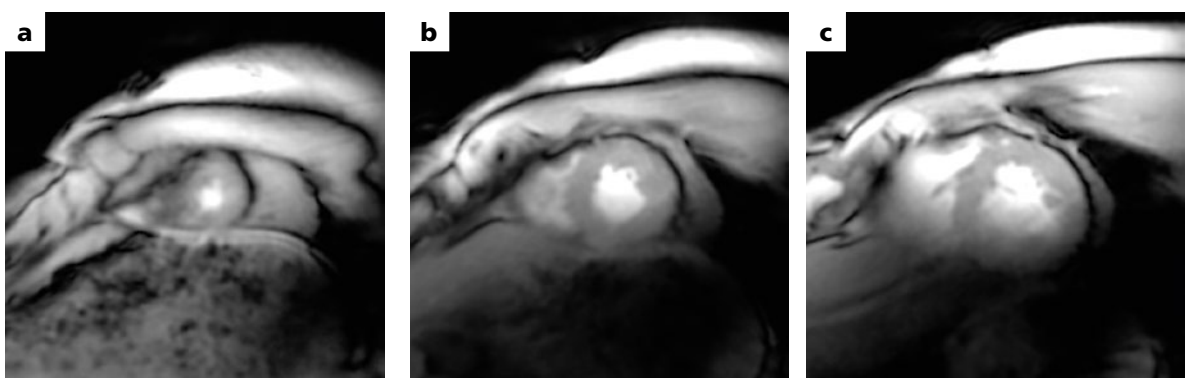
'Radiology is not a medico-technical specialty, although French administration still classifies us as such. We're a medical discipline. The old-fashioned image of the radiologist reading scans alone in a basement and not having contact with anyone else in a hospital is outdated.

'The radiologist,' he emphasised, 'is now at the centre of patient care and healthcare.' (MR)

High-resolution Simultaneous Multi-Slice (SMS) dynamic MRI of the heart at 7-Tesla

Increased signal-to-noise ratio from the 7-Tesla MRI is harnessed for refined imaging of heart. Simultaneous Multi-Slice (SMS) cardiac dynamic MRI (cine) permits the acquisition of three thin-slices (4 mm) within a 10 s breath-hold. Robustness to patients motion and limited breath-hold capacity is guaranteed through a dedicated self-calibrated SMS technique tailored for cardiac imaging. Morphologic and dynamic information of the myocardium is achieved with millimetric resolution (0.9x0.9 mm²). Strong intensity variations characteristic of 7-Tesla MRI can be observed from anterior to posterior myocardial segments.

Figure 3: SMS cine acquired within 10s showing diastole (relaxed phase of the cardiac cycle) of the apex (a) mid-ventricular (b) and base (c) slices.



New software improves prostate cancer detection

MRI tumour scans overlaid onto ultrasound

Report: Mark Nicholls

New medical software which overlays tumour information from MRI scans onto ultrasound images is helping to improve detection of prostate cancer by guiding surgeons as they conduct biopsies.

Developed at University College London (UCL), the software is deployed via a system called SmartTarget and embraces artificial intelligence (AI) to use both systems in tandem to enable surgeons to pick up clinically-relevant cancers missed when using visual detection methods.

Whilst MRI-targeted biopsies have improved detection rates to almost 90% in recent years, the UCL team believe the SmartTarget system further enhances this by allowing a 3-D model of the prostate and cancer to be created for each patient from their MRI scans using advanced image processing and machine learning algorithms. Then, during biopsy, the model is fused with ultrasound images so that surgeons can target areas of concern.

In a recent study - funded by the UK Department of Health and Social Care and Wellcome Health Innovation Challenge Fund – 129 people with suspected prostate cancer underwent two biopsies – one using the SmartTarget system and one where surgeons could only visually review the MRI scans. The two strategies combined detected 93 clinically significant prostate cancers, with each picking up 80 of these cancers; each missed 13 that the other method picked up.

As a result, the researchers report that visual reviews of MRI scans by surgeons should be used in tandem with SmartTarget because the technique enables surgeons to make subtle adjustments, such as adapting to the patient's and prostate movement as the needle is inserted.

Co-senior author Dr Dean Barratt, at UCL Medical Physics & Biomedical Engineering and UCL Centre for Medical Image Computing, who invented the SmartTarget system, said: 'We developed the system to equip surgeons with vital information about the size, shape and location of prostate tumours during a biopsy that is otherwise invisible on ultrasound images.

'The software provides a clear target. Because MRI-targeted biopsies require a very high degree of expertise and experience, we hope that the imagery displayed by SmartTarget will help to bring high accuracy prostate cancer diagnosis to a much wider range of patients and hospitals.

'In essence, the software makes tumours that are otherwise invisible on ultrasound images, visible. This reduces the need for the surgeon to rely solely on a mental model of where a tumour is, which relies heavily on skill, experience, and the ability to visualise anatomy in three-dimensions,' Barratt explained.

'The result is increased confidence, which can be particularly important for urologists who have relatively little experience in the tumour-targeted biopsy technique. Benefits for patients also include increased confidence that, using the system, their surgeon can target a tumour accurately. Tumour targeting using MRI has been shown to be much more reliable than conventional biopsy methods and requires fewer needle insertions to make a diagnosis, resulting in a quicker, less-invasive procedure.'

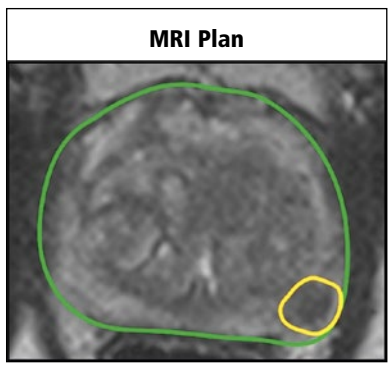
The system, he added, also requires much less data on where the boundary of the prostate lies in the ultrasound images. Consequently, the surgeon does not need to use the software to define the entire boundary, leading to a much more streamlined clinical workflow without laborious interaction that is required with other systems.

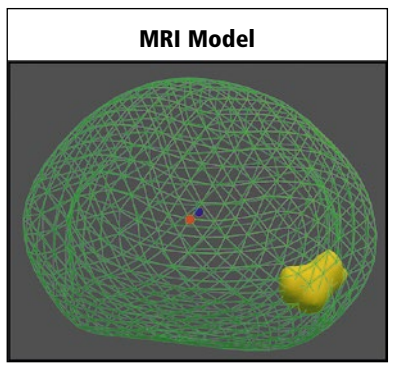
The software has been commercialised by SmartTarget Ltd, a UCL spin-out company, and is already in use in several hospitals in the UK and USA.

Co-senior author Professor Mark Emberton, Dean of UCL Faculty of Medical Sciences, said: 'With this study we now have hard data showing that SmartTarget is as good as a group of experts in targeting tumours in the prostate, and have a glimpse of how clinicians and computers will be working together in the future.'

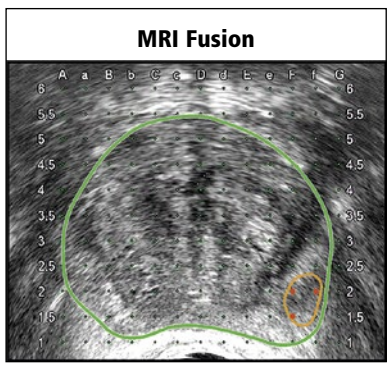
Mark Emberton is Professor of Interventional Oncology at UCL, an Honorary Consultant Urologist at University College Hospitals NHS Foundation Trust and Dean of UCL Faculty of Medical Sciences. His research aims to improve diagnostic and risk stratification tools and treatment strategies for prostate cancer, specialising in the implementation of new imaging techniques, nanotechnologies, bio-engineering materials and non-invasive treatment approaches.

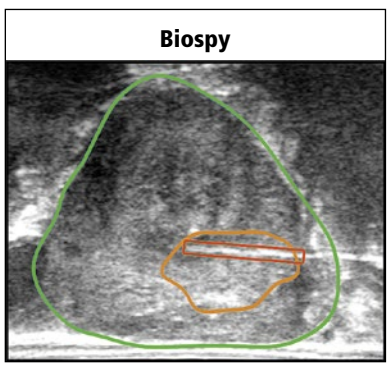
Dean Barratt is an Associate Professor in the Department of Medical Physics & Bioengineering at UCL, conducting research to develop software-based technologies to make data from diagnostic and/or surgical planning images available before a procedure, to be aligned with images obtained during the procedure to aid surgical navigation, particularly on developing image guidance methods that employ 3-D ultrasound imaging.





The four images show how SmartTarget helps to guide prostate biopsies. Step 1: Areas of suspicious tissue are identified and contoured on MRI scans.
Step 2: The SmartTarget system creates an anatomically accurate model of the prostate and suspected tumour site.





Step 3: The model is mapped onto ultrasound imaging in real-time.
Step 4: Live guidance enables real-time tracking of biopsy needle (highlighted in red) against target site

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Radiolo optimis

Report: Cynthia E. Keen

The topic of artificial intelligence (AI) was omnipresent at RSNA2018, the annual meeting of the Radiological Society of North America.

From the opening presidential address, throughout scientific sessions and educational presentations, to the vendors' technical exhibition, around 53,000 attendees learned about pioneering new products, research, plus challenges and opportunities to implement and adopt AI technology. Just as cross-imaging modalities and the digitisation of radiology departments radically impacted on this medical specialty, AI represents another sea change.

However, unlike previous RSNA events, opinions about AI are shifting from concern to optimism that the technology will enhance the profession rather than commoditise radiologists and diminish their role as physicians. In her president's address 'How Emerging Technology Will Empower Tomorrow's Radiologists to Provide Better Patient Care', Professor Vijay M Rao MD, chair of radiology at the Sidney Kimmel Medical College of Thomas Jefferson University in Philadelphia, emphasised that AI will empower radiologists to 'enhance the profession and transform the practice of radiology worldwide'.

Rao predicted that AI will perform tasks which will enable radiologists to become the primary consultant to physicians again, through the control and management of 'diagnostic data hubs' and initiation of direct radiologist-to-ordering physician communication and cross-section medical specialty partnerships that flourished during analogue film radiology reading rooms and began to disappear as PACS proliferated.

In the oration following on the AI analytics and informatics topic, Michael P Recht MD, chair of the Department of Radiology at NYU Langone Health in New York City, also underlined that AI can help radiologists become key figures in a treatment team again, leading colleagues in decisions about diagnoses and best treatment options.

Along with his discussion on the potential of AI to improve and

Artificial intelligence themes dominated RSNA2018

ogists reveal sm about AI

increase the value of radiology reports, and to enable virtual rounds and virtual consultations when needed, Recht also emphasised the need for AI use to improve data and image acquisition in real-time. He cited the benefits of deep learning algorithms with pattern recognition and image reconstruction capabilities to create quality diagnostic MRI images within five minutes, which could have a dramatic impact on report turnaround time, patient throughput and department workflow.

Better data analysis could improve overall department operations, identifying areas for improvement in interpretation accuracy, efficiency and communication. Data correlating diagnoses with clinical pathology and outcomes could be used in a continuous feedback mode to perform smarter patient imaging and improving evidence-based guidelines.

A machine learning competition

The RSNA also sponsored a machine learning competition to develop algorithms that could identify and localise pneumonia in chest X-rays. Over 1,400 teams took part in the RSNA Pneumonia Detection Challenge, and 346 submitted results for evaluation. Alexandre Cadrin-Chênevert MD, a Canadian radiologist and computer engineer at CISSSL of Saint Charles Borromée, Quebec, and Ian Pan, a third-year medical student at Brown University in Providence, RI, created the winning algorithm and received a $12,000 prize.

3-D medical printing was also emphasised in scientific presentations as well as a dedicated 3-D Printing and Advanced Visualisation Showcase. Sixteen companies participated in a 186 square metres venue, which combined educational lectures and demonstrations of products and techniques to create 3-D-printed models to improve presurgical planning and intra-operative guidance. Efforts are underway in the USA for radiologists to be compensated for medical 3-D printing, which is expected to boost utilisation significantly.

As just two examples… in a scientific session, Philipp Brantner MD, co-director of the University Hospital of Basel's 3-D Print Lab and a senior physician in cardiac and thoracic diagnostics, discussed how the use of CT data-based 3-D printed models to pre-contour implants in inferior orbital wall fracture surgery can significantly reduce operating time.

Findings from a study conducted at the hospital showed that, when such a model was used, surgical procedures were reduced from an average 96 minutes to 64 minutes. Nicole Wake PhD, of New York University School of Medicine, discussed how 3-D printed prostate models created from pre-operative MRI data can be used to correlate MRI and pathology and also help patients better understand their disease and treatment.

A nearly 60% vendor increase in the Machine Learning Showcase compared to 2017 was notable. This included numerous theatre lecture presentations, 22 interactive kiosks, and 1,496 square meters of exhibit space for 78 participating companies.

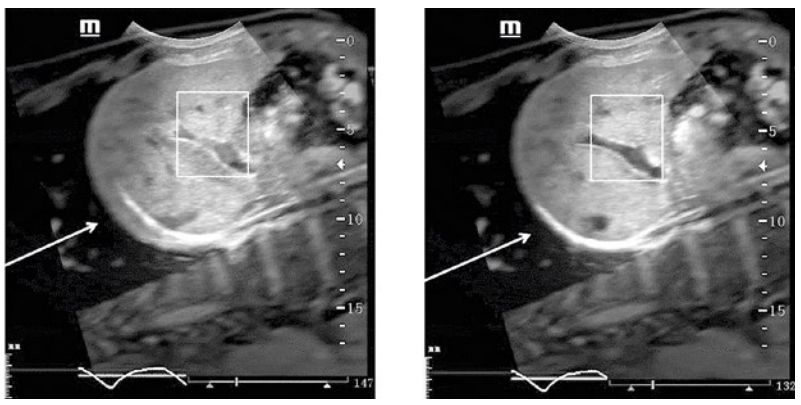
An RSNA representative told European Hospital that the specialised showcases represent the organisation's interest in emerging technologies. 'Our members have expressed interest in learning more about machine learning, AI and 3-D printing and advanced visualisation products, including augmented and virtual reality platforms. These targeted showcases represent a one-stop destination for our attendees to see and learn more about these products in an integrated setting.'

As always, clinical topics were numerous, diverse and impressive. A huge educational exhibit centre in a dedicated hall, and technical products exhibited by 732 companies in 40,300 square metres, provided the usual overwhelming data overload. Although attendance has not matched that of 2014, online digital access to 'virtual sessions' expanded through March 2019, reaches radiologists worldwide.

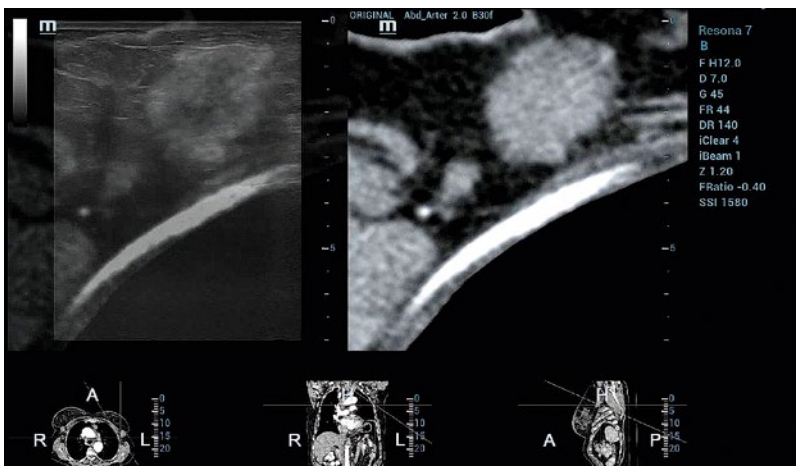
Merging the benefits of two imaging worlds

Advancing fusion imaging

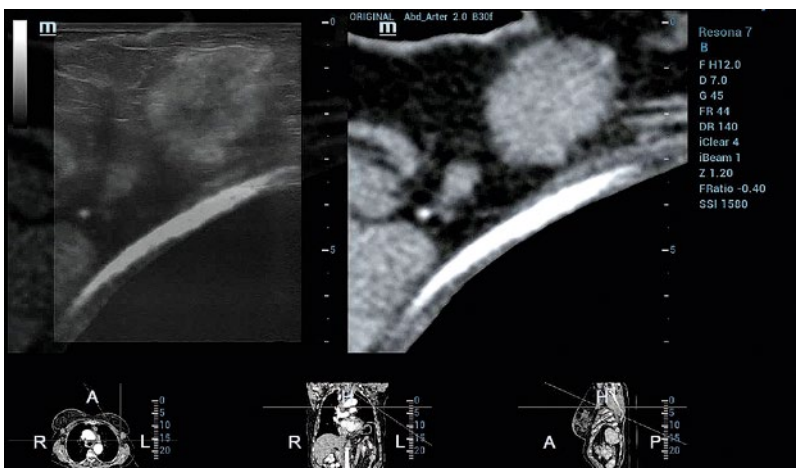
Radiologist Alexis Kelekis, Associate Professor of Interventional and Musculoskeletal Radiology at Attikon University Hospital, Athens, spoke with Daniela Zimmermann about his work and developments in merging scans and techniques to gain greater accuracy in diagnosis and planning.



The left image is without respiratory compensation, which adds an artifact during to motion of the liver during breathing (arrow). The CT image does not change, while the ultrasound image changes with the breathing cycle. On the right the ultrasound and CT image match perfectly due to iFusion respiratory compensation



To the left, the fused image of US and CT for a lymph node prior to biopsy. Right: the CT image of the lymph node. Below the CT scan and the plane projected for the specific ultrasound scanning



Same as above, adding color Doppler to the image, in order to identify the feeding vessels of the lymph node. The Doppler image is projected also on the CT image (right)

The benefits of fusion imaging are widely acknowledged. Favoured in clinical practice by radiologist Alexis Kelekis, he explained: 'The advantage of using fusion is to bring the best of two worlds together; I have the conspicuity and accuracy of the CT image and at the same time the free-hand capability of ultrasound.'

By angulating the orientation to view different slices, the radiologist can easily direct the interventional tool to the relevant region of interest. 'Or,' he adds an analogy, 'we use CT as a map on a GPS, which tells the car – which, in this context, is the ultrasound probe – where to go.'

Ultrasound does have limitations compared to MRI and CT; it is a user-dependent system, results are not perfectly reproducible, and images are not always as clear or easy to read anatomically. On the plus side, it is portable, has real-time capability, excels at smooth tissue examination, is cost-effective, uses no radiation and requires less infrastructure.

'Healthcare systems are different. In countries such as Italy or China, the system is mainly based on ultrasound diagnostic procedures, whereas CT and MR are used more in the USA and Europe.'

Yet, when dovetailed with other modalities such as CT images, ultrasound fusion imaging offers additional user control and confidence with real time imaging speed seeing the fusion of selected images of the targeted region of interest (ROI) for interventional procedure guidance.

The benefits of 'elastic' images

More recently, Kelekis has been working with Mindray and the company's ultrasound fusion imaging technology, which can combine liver ultrasonic images with previously acquired abdominal CT/MR images in real time and in an overlapping manner. By integrating the information from CT/MR, sonographers can pinpoint lesions during ultrasound intervention.

When using fusion imaging, Kelekis pointed out, a challenge for clinicians lies in registering an image from one modality with another. 'The patient in the CT scan cannot be in the exact same position as with ultrasound, so the two images are mismatched. In order to do the matching, the technician/doctor tries to bring them together or the machine does that automatically. There are different algorithms that will do that registration and figure out the different densities of tissue to match those tissues together.'

A middle-ground option, and one gaining popularity, is semi-automatic registration, where a system will bring tissue together but leave doctors to do the final editing manually.

'What will be interesting to see in the future is 'elastic registration', which means the system will deform the CT or ultrasound image to get them to fit together better.'

The professor's department has collaborated with Mindray in using iFusion in clinical practice. 'It is an interesting tool and means we have a very accurate software to go in specific places and use fusion in cases where the approach was more difficult under CT. At the same time, we helped to develop the software and make it more user-friendly. The result is a better tool for doctors, a more precise approach for fusion imaging, and a more seamless logistical approach.'

His team also worked with Mindray to develop a logistical structure on how to teach technicians and clinicians to move through the procedure of registering and fusing images in a faster, more efficient way, to help optimise the use of clinical time.

Treat the disease, not just an organ

He believes there is potential for future development in fusion imaging as computers become more powerful in handling greater volumes of data. 'At some point, we will be able to scan the whole body in CT, then in ultrasound and after that, match data volumes together to have a complete fusion of the whole body. With more computer capability in handling data information, that will increase the possibility of interpretation.'

As a radiologist and imaging specialist, he explained that, for example, in liver disease diagnosis and treatment, a whole-body CT and US scan is important. 'Patients with liver lesions have bone lesions and other metastases, so we do not treat an organ, we treat a disease. All these imaging systems will allow us to get to the site we want to treat, wherever that is, in a more precise and less invasive way.'

Using ultrasound in conjunction with CT means the radiologist can guide the focus to specific areas. 'I can match those examinations with iFusion and use previous CT scans to match the new ultrasound image, so I can marry different time sequences using information from one with information from another.'

Integrating such large amounts of data with PACS systems, he suggests, is relatively straightforward today and the system also facilitates more efficient treatment planning protocols. 'With protocol planning it's important to decide when you are going to do the exam and how you are going to register that exam,' Kelekis explained.

Alexis Kelekis is Associate Professor of Diagnostic and Interventional Musculoskeletal Radiology in the Radiology Department II at the University of Athens. He specialises in MSK and spine imaging, for which he also gives undergraduate teaching courses at the same university. Kelekis is a reviewer for several radiology- and spine-centered journals, has written a great number of scientific publications and is member of many radiological societies, including the Greek, Belgian, Swiss and North American Societies of Radiology, the Society of Interventional Radiology and Cardiovascular and Interventional Society of Europe.

'We've been using specific protocols and training our technicians to do the fusion and preparation for a whole procedure so, when the doctor arrives, the whole registration process has already been completed and the physician is ready to move on directly to the interventional examination.'

New minds are open for new ideas

While these tools offer important benefits, he acknowledges that, persuading people with different mindsets, approaches and workflows to adopt them, may be a challenge.

However, he is optimistic: 'With the technological advancement we have in our everyday lives, people are becoming more flexible to change and I hope these changes will pass more easily into our medical world.'

Kelekis acknowledges the inevitability of Artificial Intelligence (AI), which he is already using in his department, such as with auto-count systems for breast lesion or lung nodule recognition for diagnostic services. He said such systems will become 'cleverer' but will not replace doctors and the role the human brain plays in diagnosis.

'In the future, as long as fusion expands, we will have more assistance,' Kelekis confirmed. 'Technology that can help us do that in a more seamless and user-friendly way to speed up the processes will be very effective.'

High diagnostic res. with minimum exposure

Launching new CBCT technology

A pioneer in CBCT imaging, NewTom has introduced the only CBCT system with an open gantry and supine positioning, the manufacturer reports. 'Exceeding the limits posed by CT systems, the NewTom 5G XL combines high diagnostic resolution with minimum patient exposure.'

Unlike its MSCT counterpart, CBCT technology can generate ultra-high definition volumetric images of bone tissues, with 'native' isotropic voxel resolution, non-overlapping sections and fewer artefacts, New Tom continues. 'The 5G XL opens the door to radiologists and specialist physicians who require the best possible diagnostic capabilities in ultimate quality 2-D and 3-D. In addition to examination of dental-maxillofacial pathologies, it's also possible to examine the internal ear, fully analyse airways and maxillary sinuses and diagnose chronic or traumatic pathologies involving bones, joints and the spinal column for more in-depth orthopaedic investigation.'

NewTom is at ECR 2019
Expo X1. Booth N.115

Practical videos, e-booklets, case studies and more

Online education in vascular ultrasound

Fabrizio d'Abate, St. George's University Hospitals NHS Foundation Trust, in London, UK describes new aspects of learning and training in ultrasound operation

A textbook represents the most traditional tool of a teaching arsenal. However, the I T boom and internet have transformed the way people approach different tasks in their lives, from solving a problem to acquiring knowledge. This has influenced the way of learning, that has become more dynamic and interactive.

Never before has education been available on a large scale as it is now, with so much information and knowledge to convey to learners. Online courses are increasingly necessary for education 'becoming not an add-on feature in teaching but a necessity'.

With online education users can proceed through a training program at their own pace, can access the training at any time, receiving only as much information as they need in an interactive way. The number of people opting for online courses worldwide is increasing due to busy lifestyle.

Ultrasound is a fast growing diagnostic technique and is in constant demand, however, there remains a shortage of experienced operators in such a field, especially in vascular ultrasound.

The lack of a dedicated e-learning teaching platform in vascular ultrasound and the common passion in education shared by a vascular sonographer and a cardiovascular medicine doctor, gave life to www.abcvascular.com a new e-learning platform to support healthcare professionals who want to acquire knowledge and skills in vascular ultrasound.

The ABCvascular mission is to walk learners through all the steps necessary to learn vascular ultrasound, from the foundation notions (the ABC of vascular ultrasound), to the more advanced concepts used to diagnose vascular diseases, simplified into key learning points to make learning fast and easy.

The courses are supported by commented video-lectures where split screens are used to show patient positioning, operator's hand/ultrasound transducer movements and ultrasound videos. This method of teaching is essential, as the information to acquire is inherently visual and dynamic. The aim is to offer learners a virtual experience of a one to one learning session with a vascular ultrasound expert. Learners are then challenged with real life case scenarios, where the explained diagnostic criteria are applied and explained. This will give the learner a virtual experience of vascular ultrasound in several vascular conditions. All courses and content of www.abcvascular.com have been accredited by the EACCME (European Accreditation Council for Continuing Medical Education) to provide CME credits.

Ultrasound training exoert Fabrizio d'Abate

Explanations allay patients' concerns

Effective communication on radiation risks

Communicating radiation risks is not only a legal requirement, it is also a moral obligation, asserts Dr Shane J Foley, radiographer and assistant professor at the UCD School of Medicine in Dublin, Ireland. Passing on radiation information has its pitfalls, but several helpful tools can improve communication, some of which the expert highlighted during ECR 2018.

Report: Lena Petzold

'When it comes to radiations risks, as experts we should be the linchpins for communication, because we should know exactly the risk associated with the task we are performing,' Foley stresses. 'Unfortunately, this is not the case, as multiple studies show. There's quite a difference in understanding even between experts. So, we should all go back to basics and increase our own knowledge, because how do we expect to impart information to patients if we don't comprehend it ourselves?'

Radiation risks are generally associated with either one of two categories: stochastic effects or tissue reactions. 'While we should be aware of tissue reactions, they are rather uncommon. Current evidence suggests there are between one in 10,000 and one in 100,000 cases and those are mostly skin effects. The main stochastic risk in all our practice related to ionising radiation is that of potential cancer development.'

Successfully conveying information to patients

Cancer is a disease that spreads fear in a flash, so Foley's advice is to begin a discussion with patients by highlighting the benefit of the examination and its medical need, so as to remind and reassure patients of the procedure's value.

Throughout any patient conversation it is important to use simple, plain language and focus on a few key points, instead of overwhelming patients with medical terms. Foley also recommends building and using a set of standardised terms.

Besides these basic facts, Foley also offers more personal advice: 'Minimise the use of numbers and stats,' he advised. Even though parameters such as effective dose will hold up for comparison, they can be rather confusing for patients who are rarely well acquainted with radiation effects and statistics.

Lifetime risks and natural radiation

There are more useful tools for conversations with patients such as the comparison of natural risks. 'We are very concerned with the small increased risk of cancer through radiation procedures, yet we all have quite a high natural risk of developing cancer over a lifetime anyway,' he points out. The natural cancer incidence is one in three for men and one in four for women. 'But even a relatively high dosage exam, such as a CT, still only changes a man's risk of developing cancer to one in 2.9955. That's a very small additional risk.'

For some patients it can be beneficial to talk in detail about lifetime risks. Low dose exams like an X-ray of an extremity are very hard to differentiate from other background risks, which is why the additional lifetime risk of developing cancer for such a procedure is below 1 in 1,000,000 and therefore negligible. 'Even the highest dose exams that we deliver are still classified as a low risk event,' the lecturer explains.

Japanese radiation survivors

Therefore, using those terms and statistics could help to assuage fears, yet there are also some downsides. 'All of these lifetime risks are based on extrapolations, so they are not precise. They are predominately based on the data we acquired from the Japanese bomb survivors, so a very different population exposed to a large amount of radiation in a short period – which is essentially quite different from what we are doing.' Furthermore, worried patients might easily see themselves as the one in a million case, the assistant professor warns.

A helpful tool for patient information could lie in illustrating natural radiation exposure. 'We are all naturally exposed to a certain level of radiation every day through cosmic rays, radon in the ground or consumed food,' Foley points out. Explaining to patients that ionising radiation is unavoidable puts an examination into perspective. Especially, since there is a large variation in exposure between different regions and countries, yet 'we would never consider not living in a certain area because of a small increase in radiation exposure'.

Creating a link to personal activities could also help with patient communication. 'Many ordinary activities are associated with significantly higher lifetime risks than individual diagnostic radiation exposures. We know, for example, that air travel is associated with a small increase in radiation dose, about 0.005 mSv per hour of travel, yet we think nothing of going on multiple plane trips every year,' says Foley. 'A chest X-ray is related to a lifetime risk of 1 in 1,000,000, which is the same risk as smoking 1.4 cigarettes, drinking half a litre of wine, driving 300 miles, or cycling 10 miles.' All these activities are common practice, yet no one is overly concerned with the increased risk of death they are tied to – and they do not even feature a clear medical benefit in return. Comparing a diagnostic procedure with these everyday activities that patients can relate to, levels out the perceived risk it poses.

'We have to find those measures that hit home with patients,' Foley emphasises, 'then we can allay fears'.

Personalising the communication approach is important. 'We have to be happy to use a range of methods depending on the patient's ability and understanding as much as on our own.' Furthermore, communication is never a one-way process, Foley concludes. Listening to patients' concerns and responding to questions is just as important as finding the right tools to impart information.

Examination	Equivalent to background radiation	Lifetime risk of cancer per exam
Chest, teeth, extremities	Few days	NEGLIGIBLE RISK <1 in 1,000,000
Skull, head, neck	Few weeks	MINIMAL RISK 1 in 1,000,000 to 1 in 100,000
Hip, spine, abdomen, pelvis	Few months	VERY LOW RISK 1 in 100,000 to 1 in 10,000
IVU, CT	Few years	LOW RISK 1 in 10,000 to 1 in 1,000

The level of radiation from a specific (X-ray) examination compared to the equivalent period of natural background radiation shows that, even with a higher dose examination such as a CT scan, the added lifetime risk of developing a radiation-inflicted cancer remains low

Assistant professor **Shane J Foley PhD** lectures at the UCD School Of Medicine in Dublin, Ireland, where he gained his bachelor degree in radiography in 1999. Following this he worked as a radiographer and later senior radiographer in the Mater Misericordiae Hospital, Dublin, and was involved in numerous clinical research projects. His lectureship in Diagnostic Imaging began at UCD in 2007 and Foley is now director of the BSc radiography programme. He gained his PhD in 2013 and is a member of various associations and committees, including the European Federation of Radiographer Societies.

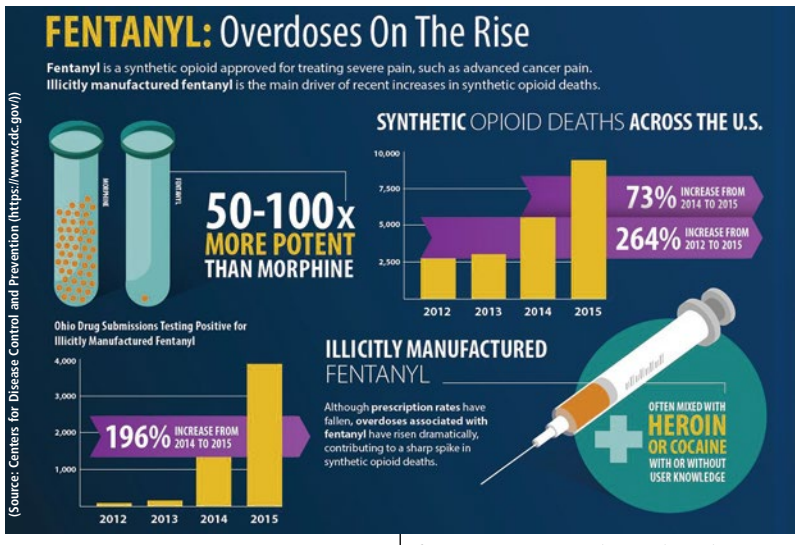
Credit for chart and illustration: NRPB (2001). X-rays how safe are they? An information leaflet for patients prepared by the National Radiological Protection Board, College of Radiographers, Royal College of Radiologists and Royal College of General Practitioners (www.hpa.org.uk).

A powerful tool to differentiate opioids

Mass Spec detects illicit drug presence

As a synthetic opioid approved for treating severe pain, fentanyl has shown clear medical benefits. However, in recent years, continuous abuse of fentanyl and its derived analogues substances has become a major public health issue – overdoses and deaths associated with illicitly-manufactured fentanyl rose dramatically. Some of these synthetic analogues have extremely high potency and only require a small amount for accidental overdose (image shows the difference in amount of a lethal dose of heroin vs fentanyl vs carfentanyl). Drug dealers have exploited this, using traces of fentanyl to increase potency in other drugs to reduce costs. These analogues are structurally similar to fentanyl, so they often go undetected. Mass Spectrometry (MS) has emerged as a powerful tool to differentiate drugs, and has particular applications in Emergency Departments where speed is often vital.

Dr Pierre Negri from SCIEX – which offers a variety of LC tandem mass spectrometry solutions in forensic and toxicology analysis – said that because people began buying drugs containing fentanyl from dealers and overdosed, the need grew to develop methods to quickly detect small amounts of fentanyl so that first aid responders could take appropriate actions. Where MS offers a solution is in its characterisation of various molecules (including drugs) as a highly sensitive and accurate analytical technique capable of providing qualitative and quantitative analytical data on extremely small amounts of analytes.



The continuous abuse of fentanyl and its derived analogue substances continues to be a serious public health and safety problem.

'As a result, mass spectrometry can differentiate drugs by assessing their mass, or molecular weight, hence providing the necessary information to elucidate their molecular structure,' continued Negri, who is the SCIEX lead for global technical forensic marketing. 'This technology can be used to detect and quantify fentanyl and its analogues in small quantity while elucidating the chemical structure of these compounds.'

Today, LC tandem mass spectrometric analysis (LC-MS/MS) is the preferred method of analysis for forensic over traditional techniques, for both screening and conformation purposes. Immunoassays are commonly used as a first-line screening method abused drugs detection and rely on the presence of a specific antibody or specific antigen in urine, blood or other fluids, yet they lack sensitivity in detecting designer drugs and require additional confirmation, which slows the analytical process.

'The advantages of LC-MS/MS over conventional methods are that it has better compound detection sensitivity for significantly lower levels than the current cut-off levels; faster time to results, with less sample prep and no derivatisation; saves time and money with multiplexing capabilities to analyse for many compounds in a single analysis; and has the ability to simultaneous quantify and identify many drug targets in various sample matrices such as saliva, urine, blood or hair samples.

'It's important to note that, as with immunoassay, assay design is crucial for accuracy and specificity with mass spectrometry. However, unlike immunoassay-based detection, mass spectrometry provides analyte specific results and allows accurate quantification of the drugs analysed with far greater sensitivity and resolving power than immunoassay.'

In recent years, mass spectrometers have become more accessible, cheaper to purchase and operate, and easier to use.

Additionally, new MS-based workflows can be developed to eliminate a two-stage process currently used for drug monitoring, by allowing technicians to run many tests at once with a high throughput, cutting processing time while improving screening accuracy with quality assurance. Negri suggests that, at present there remains a lack of reliable and inexpensive tests that allow for comprehensive surveillance of synthetic drugs flooding the illegal market, whereas the development of novel MS-based screening techniques have led to the rapid and accurate identification of fentanyl, as well as other drugs of abuse, previously difficult to detect by traditional analysis. He said the SCIEX X500R QTOF is a powerful tool for forensic researchers investigating samples for unknown compounds, drug metabolites, unknown chemicals or hazards, or novel psycho-active substances that have never been previously detected or characterised. Powered by the user-friendly SCIEX OS software, it can redefine how to analyse a routine forensic drug screening sample. The 6500 QTRAP or 6600 TripleTOF technologies can assist with research and method development.

'The versatility of modern mass spectrometers enables specific and comprehensive measurements that allow drug detection with a high level of sensitivity and specificity,' he said. 'The implementation of this technology in drug screening over the years has shown improved accuracy, precision, sensitivity, selectivity, and clinical utility over simple direct and complex reference immunoassays.'

Where seconds matter, Negri added, being able to correctly identify the fentanyl analogue screened, is critical (MN)

Dr Pierre Negri leads global technical forensic marketing for SCIEX, collaborating with opinion leaders in forensic and criminal toxicology research to develop and implement new mass spectrometry methods. In the laboratory he also works with customers to develop and promote novel mass spectrometry analysis workflows applied to controlled substances and trace evidence materials.

Towards a clearer view of complex lab results

Shaping post-analytical interpretive tools

Interpretation of complex profiles of laboratory results can be significantly improved via multivariate pattern recognition software, Mark Nicholls reports.

A multivariate pattern recognition software, developed by a team led by Dr Piero Rinaldo at Mayo Clinic in Rochester, USA, aims to integrate results to diagnose a particular condition in a single score, in an objective evidence-based way that is open to worldwide collaboration and data sharing.

Currently co-director of the Biochemical Genetics Laboratory and vice-chair of Information Management in the Department of Laboratory Medicine and Pathology at the Mayo Clinic, Rinaldo outlined the work at the Frontiers in Laboratory Medicine (FiLM) conference held in Birmingham, UK, in January.

Explaining how the software produces post-analytical tools available on demand through a web interface, the approach was first applied to newborn screening, and has grown to involve 269 programs in 69 countries.

In his presentation 'Personalised reference ranges; developing individualised reference ranges', Rinaldo suggests there are 'limitations and pitfalls' of the traditional way to establish reference ranges and cut-off values for laboratory tests.

'In my view,' he said, 'it's being done in a manner that seriously underestimates the role of covariates like age at collection and sex. For so many markers, we use the same decision limit for a 21-year-old healthy male and for an 80-year-old obese female as well.'

Moving forward, he advocates the CLIR (Collaborative Laboratory Integrated Reports) approach and the importance of individual reference ranges, paving the way for how lab tests should be routinely ordered in the era of personalised medicine.

CLIR, he said, replaces conventional reference ranges with continuous covariate-adjusted percentiles; replaces analyte cut-off values with condition-specific disease ranges; enhances the clinical utility of individual markers with all possible permutations of ratios, and replaces diagnostic sequential algorithms with tool-based parallel algorithms.

However, he stressed: 'The important point to recognise here is that creating better reference ranges is just one initial step of the process, not the end point. That's the post-analytical interpretive tools.'

The basic tenant of CLIR is worldwide collaboration and data sharing to establish covariate-adjusted reference ranges based on millions of data points and disease ranges.

'The software evaluates the degree of overlap of any marker (after covariate adjustment) between the two ranges separately for every possible target condition, and use it to compile a cumulative and integrated score. The comparison of this score versus those calculated for known cases offers an objective assessment of the disease likelihood, a vast improvement over the binary choice of normal/abnormal.

'The other relevant concept is that clinical validation is an evolving process, as new cases are added (daily) to the database the tools improve accordingly, such as via machine learning.'

CLIR was originally developed to support Region 4 Stork (R4S), a USA federally-funded collaborative project that started in 2004 aimed at improving newborn screening by tandem mass spectrometry.

In that project, cumulative reference intervals of dozens of amino acids and acylcarnitines were derived from some 30 million newborns tested in 69 countries, disease ranges were compiled from >21,000 true positive cases.

Since 2012, R4S and CLIR online tools have been utilised more than half a billion times, with an average of more than 200,000 scores calculated daily worldwide.

In recent work showing the first prospective application of the second generation of the software, the team focused on the implementation of newborn screening for lysosomal disorders, an area where there has been overall poor specificity, psychosocial harm experienced by caregivers, and costly follow-up testing of false-positive cases.

The study concluded that: 'Post-analytical interpretive tools can drastically reduce false-positive outcomes, with preliminary evidence of no greater risk of false-negative events, still to be verified by long-term surveillance.'

While the outcome of the R4S project was a false positive rate (FPR) of 0.024% and a positive predictive value (PPV) of 69% (US average ~20%) while the first application of CLIR to three lysosomal disorders achieved a FPR of 0.001% and a PPV of 87% and has led to the discovery of a novel biomarker.

'This work has paved the way to the pursuit of precision new-born screening, which is defined as near-zero FPR preceding any confirmatory use of molecular testing,' Rinaldo added.

The software offers a number of benefits for clinicians. 'In the context of newborn screening, a substantial reduction of false positive outcomes means better utilisation of health professional time and resources (no need to see patients who don't need to be seen), and prevention of unnecessary follow up testing.'

Significantly, it reduces unnecessary stress to parents that something 'may' be wrong with their baby when the screening can clarify this.

Born in Venice, Italy, **Dr Piero Rinaldo** is a Professor of Laboratory Medicine and the T. Denny Sanford Professor of Paediatrics. He received his medical and research training at the University of Padova, in Italy (1977-1987) and Yale University in New Haven, Connecticut (1987-1998). A paediatrician, board-certified in Clinical Biochemical Genetics, he co-directs the Biochemical Genetics Laboratory and is vice-chair of Information Management in the Laboratory Medicine and Pathology dept at Mayo Clinic, Rochester, Minnesota.

Unleashing the power of digital pathology for precision medicine

AI for digital pathology is still an 'emerging science'

Digital pathology, combined with the power of Artificial Intelligence (AI), is one of the most promising fields for the delivery of precision medicine.

In the first keynote address for the 5th Digital Pathology & AI Congress (Europe) held in London last December, Professor of Pathology, Marilyn Bui, focused on how digital pathology is impacting on precision medicine.

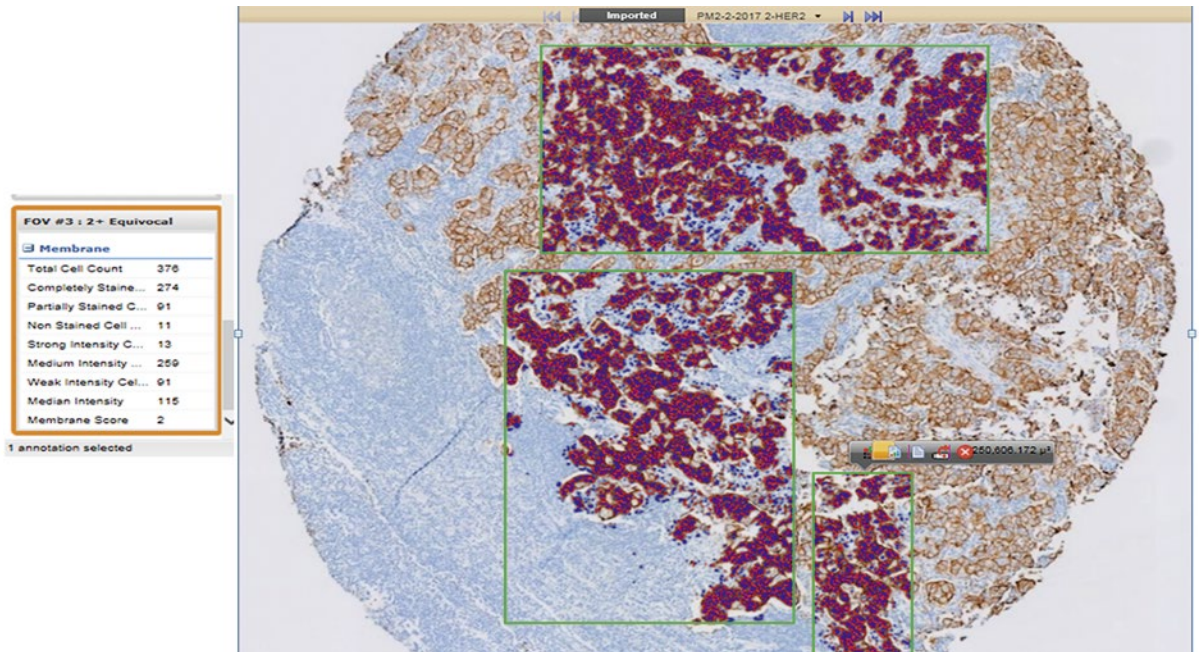
During her address, 'Unleash the Power of Digital Pathology and Artificial Intelligence for Precision Medicine', the professor outlined how digital pathology provides connectivity and accessibility by combining with image analysis and AI, leading to improved quality and efficiency and transforming pathology data into clinically actionable knowledge to help deliver precision medicine.

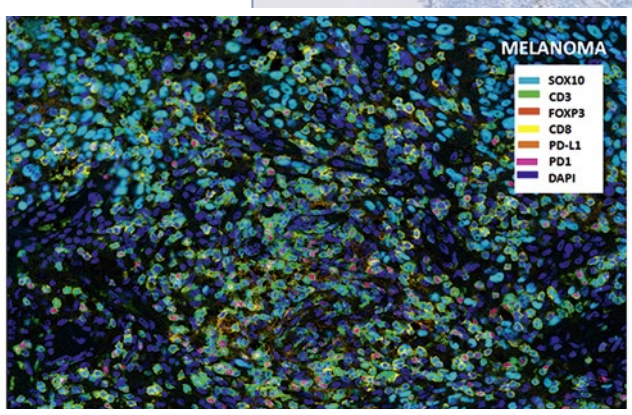
The next phase of advanced imaging analysis combined with AI is a 'game changer' in advancing the field, she added.

'It allows pathologists to look deeper into the data than ever before and to get more information and quantify the information by automation,' said Professor Bui, 'Image analysis and AI is the Holy Grail of digital pathology. The next step is to integrate digital pathology information and patients clinical and omics data to make novel information accessible to the clinical team, which gives the pathologist augmented ability to deliver patient care.'

While acknowledging that digital pathology and AI was still an 'emerging science', she told congress delegates that the digital pathology and AI was the key component for advancing personalised medicine and encouraged practitioners to move into the field and leverage this technology.

In tandem, Bui pointed out, in this, that vendors are now rapidly developing support for pathologists. 'Pathologists are the leaders in precision medicine by providing forecast of diagnosis, prognosis and prediction of the therapeutic response,' she explained.





A screen shot of quantitative image analysis (QIA) of a breast cancer biomarker human epidermal growth factor receptor 2 (HER2) immunohistochemical (IHC) testing by a FDA-approved commercial platform. Image: Marilyn Bui

Left: A digital image of a multiplex immunostain of a melanoma sample showing multiple biomarkers are studied simultaneously on one tissue section by fluorescent in situ method which generates enormous amount of information. Bui explains that this type of image data analysis is beyond the ability of the naked eyes of human and manual scoring, while computational/algorithm-based image analysis developed with pathologists' input provides a very powerful solution. Image is courtesy of Susan McCarty of Mofitt Cancer Center.

AI, Bui agreed, is the 'third revolution' in pathology, after the advances of immunohistochemistry in the 1980s and molecular pathology and next generation sequencing in 2010, with the first digital scanners for primary diagnosis approved by the FDA in 2017.

'But now, the time is different: there's a huge amount of data, far beyond human capability to handle it. Computer speed, storage and sophistication is maturing and the whole digital ecosystem is in favour of digital pathology application.'

Pathologists, Bui believes, should be willing to embrace these changes, ready to lead and participate in the innovation and advance of safe AI introduction into practice, because AI delivers on detection, quantification, classification (such as tumour group and type), prognosis (in terms of combining clinical and genomics information) and prediction.

'This is where AI will shine,' she said. 'With image analysis, it improves quality and efficiency and transforms pathology data into clinically actionable knowledge – and we can make all this information accessible to human action.'

Bui looked at the advantages of deep learning in breast pathology – such as the CAMELYON 16 and 17 challenge – prognostication criteria for diffuse gliomas, classification and mutation prediction for lung cancer, and precision immune-profiling for various cancers.

'Multiple studies have proved the concept that the digital pathology approach exceeds the accuracy of the highly-trained human expert in terms of predicting tumour classification and clinical outcome, which will impact on putting the right patient on the right treatment path.'

AI and digital pathology, she said, also has benefits in clinical trials and drug development by, for example, extending the ability of a pathologist to study a tumour. The data can be mined for so many purposes.

However, while highlighting the advantages and potential of digital pathology, Bui also pointed to the existing barriers to digital pathology adoption: regulatory, financial, technical and the culture within the discipline.

Regulatory agencies, such as the FDA, oversee certification to ensure quality and reliability of the imaging system into the market.

However, pathology professional societies, such as the College of American Pathologists, set general guidelines on how to validate the imaging system to ensure the consistency of diagnosis made by pathologists using the systems.

Breaking the financial barrier lies in providing the evidence that digital pathology is more efficient and effective – Bui points to evidence suggesting 12-13% more efficiency; saving on retrieval of archived slides; opportunities to merge lab and pathology departments; how reduced turnaround times can change patient pathways and the way digital pathology facilitates review and improves diagnostic accuracy.

In terms of technology, image quality and software issues still need to be ironed out in some respects, while speed, file storage, and IT structures remain a key component.

A promising advance, she noted,

Seeking answers to combat Middle East respiratory syndrome

Emerging MERS-CoV research


Shutterstock/Lukiyanova Natalia frenta

With a case fatality rate of 35 percent, a Middle East respiratory syndrome-related coronavirus (MERS-CoV) infection – also called camel flu – is a dangerous disease.

About seven years ago, when the virus was first isolated, mortality was close to 100 percent since only severe infections that led to the patient being in intensive care were recorded. Today the environment of each victim is epidemiologically examined. This close monitoring 'has shown that not all MERS-CoV infections are extremely severe, particularly in younger patients the course of disease can be less damaging,' said Austrian virologist Professor Norbert Nowotny, who updated European Hospital on these viruses at the International Meeting on Emerging Diseases and Surveillance (IMED).

The first MERS case was reported in 2012, in a man who had died of severe pneumonia. A previously unknown coronavirus, related to the SARS coronavirus, was isolated. To date, all reported MERS-CoV infections in humans have originated on the Arabian Peninsula.

However, due to international travel these spread to 257 countries. By 31 December 2018, a total of 2,279 cases were reported, 806 of those were fatal. The major symptom is severe lung disease, but the course of the infection depends on the age of the patient: the older the patient, the more severe the infection. In addition, pre-existing conditions such as diabetes and overweight are crucial factors.

Nowotny was a member of the research team that discovered the virus is present in dromedaries (camels) and that the infections are a result of a zoonotic event. Almost all older dromedaries are seropositive, i.e. they were exposed to MERS-CoV at some point in their lives. Dromedary calves are protected by maternal antibodies for about three to four months; then the calves are infected with the obviously widespread virus.

In dromedaries, the infection is mostly asymptomatic, some show a low-grade rhinitis. During the acute period of the infection, which lasts about one week, the animals excrete large numbers of the virus via nose and eye secretion. Transmission to humans most likely takes place during this short period and requires close contact with the animal, Nowotny pointed out. 'Contact with dromedaries aged about three to 18 months poses the largest risk.' However, only five percent of the infections in humans can be traced to direct contact with dromedaries – in most cases the virus spreads via person-to-person transmission.

Currently, there is no commercially available vaccine. 'In view of the rather low number of cases, a vaccine might not make sense at all,' Nowotny suggested. People who handle dromedaries on a day to day basis might benefit from an injection but, for the population at large, it is superfluous – which includes tourists as long as they follow Nowotny's

Marilyn Bui is Professor of Pathology and President of Medical Staff and Director of Analytic Microscopy Core, Moffitt Cancer Center, Tampa, Florida. She is chair of the College of American Pathologists (CAP) Guidelines Committee Expert Panel for Qualitative Image Analysis of HER2 immunohistochemistry for Breast Cancer, also vice-chair of the CAP Digital Pathology Committee and President-elect of the Digital Pathology Association and editorial board member of the Journal of Pathology Informatics.

is a willingness among healthcare professionals and industry to work together to improve the way healthcare computer systems share information and create improved interoperability for digital pathology imaging.

The culture among practitioners, however, remains a hurdle. Bui suggested a way to overcome this by embracing a planned and phased adoption strategy and to be willing to learn from early adopters.

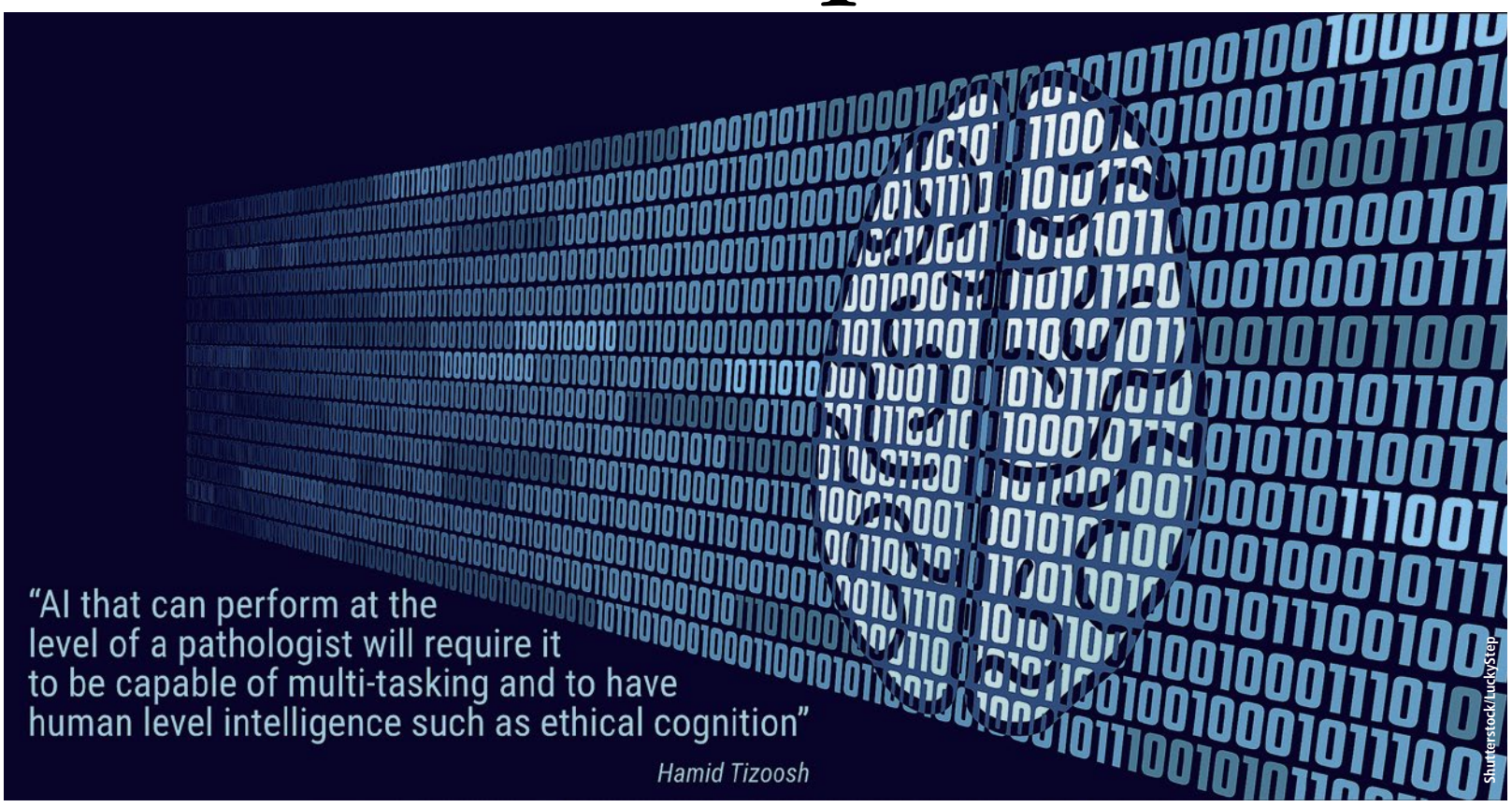
Nonetheless, there are many opportunities offered by digital pathology and AI.

'In the area of precision medicine, the role of pathologists has been increased because now we have augmented ability to produce impactful data for the clinical team.

'Finally,' she concluded, 'digital pathology and AI are here to stay and will continuously transform the delivery of precision medicine. Collaboration of pathologists, scientists and industry are important to move the field forward in a meaningful way and each individual can make a difference and be a catalyst for change.' (MN)

Bridging the gap between pathologist and algorithm

A human will always be in the loop



Digital pathology can gain huge benefits from rapid image search and the effective extraction of knowledge from large medical archives via artificial intelligence (AI).

It facilitates identification of anatomical and pathological similarities, significantly enhances the clinical workflow, and ultimately paves the way for more informed diagnosis and better patient outcome.

Effective archive searching bridges the gap between computer algorithms and pathologists, adding a new dimension to clinical practice in an ever-more demanding working environment.

Learning to search in large image archives

The subject was explored in the keynote presentation 'Learning to search in large image archives: how AI agents can serve pathologists' delivered by Dr Hamid Tizhoosh, at the Digital Pathology and AI Congress in London this December.

Despite shortcomings, could AI replace the pathologist?

Tizhoosh, from the University of Waterloo in Ontario, Canada, and director of the Knowledge Inference in Medical Image Analysis (KIMIA) Lab, outlined how AI uses software algorithms to represent data, classify data, and search for similar instances, either in a supervised way (with a pathologist's direct and indirect instructions) or non-supervised.

'Learning is just distance minimisation between what AI is calculating and what pathologists have put forward as labelled or annotated data,' he explained.

The deep learning aspect of AI has proved most effective in this respect with the ability to classify images (such as deciding whether an image is cancerous or not, or adding grading); segment by focusing on a specific part of the image; or search the archive to unearth similar cases.

'Image search is the unsupervised part,' he said, 'because you do not need a pathologist to teach the software about what to do.'

Whilst he highlighted AI shortcomings, he also posed the question as to whether AI can ultimately replace the pathologist. 'The answer to that is no,' Tizhoosh confirmed. 'AI is not at the stage where it can write a pathology report but you can use AI to search and find similar cases so that the pathologist can write a better report.

'The human operator is the ultimate validation of AI, so that means there will be no full automation and the human will always be in the loop from the beginning – either to teach, validate, accept or reject.

'You cannot replace the pathologist because AI is still very weak and it is the pathologist who writes the detailed report, whereas AI just gives a simple answer. Algorithms cannot provide explanations such as why it came to a decision, or why do you think the image depicts cancerous regions.

'Artificial intelligence application is just to assist. So, asking whether AI can replace the pathologist is not a serious question.'

AI must be able to multi-task and have human level intelligence

To truly have AI that can perform at this level will require it to be capable of multi-tasking and to have human level intelligence such as ethical cognition, he pointed out.

However, the existing benefits are significant with AI able to rapidly search out similar cases with annotated information. A big advantage of this is the element of 'virtual peer review' because many of the reports in the archive will be from different pathologists.

Needed: around a half million images

'AI can access the knowledge of colleagues even when they are not there, but you need a large archive of images for that, let's say, upwards of half a million,' Tizhoosh said. For an image search in such large archives to be effective, bar-coding (binary tagging) is the key step.

'You can search half a million scans a second,' he continued. 'What you can't do is bring up 500 glass slides from the basement and search through them – this is where we really start to think about the advantages of digital pathology and if you have a large enough archive the search can really contribute to consensus.' (MN)

Hamid Tizhoosh is director of the Knowledge Inference in Medical Image Analysis (KIMIA) Lab in the Engineering Faculty at the University of Waterloo. He is also a member of the Waterloo AI Institute, and a faculty affiliate to the Vector Institute. As part of his commercial activities, he is presently the AI advisor of Huron Digital Pathology, St Jacobs, Canada.

two golden rules: 'Don't get too close to young dromedaries and if you ride on an adult dromedary wash your hands afterwards with any commercially available disinfectant.' It was also suggested to vaccinate young dromedaries in order to break the infection cycle.

However, there are questions on MERS-CoV that remain to be answered: Dromedaries are infected not only on the Arabian Peninsula but also in Africa and Iran – so why have all human cases reported so far originated on the Arabian Peninsula? One theory is that there are regional genetic differences. Moreover, diagnosing the disease is not always easy, and on the Arabian Peninsula dromedaries are pets, rather than farm animals as in Africa – which means closer contact.

But even the infection path among dromedaries is far from clear as Nowotny explained. 'Is the virus limited to dromedaries or are other animals involved, such as ticks or small rodents?' These questions the Austrian virologist is currently working to answer.

Dr Norbert Nowotny is a professor at the Institute of Virology at the School of Veterinary Medicine in Vienna and at the College of Medicine at the Mohammed Bin Rashid University of Medicine and Health Sciences in Dubai (UAE). The virologist's research focuses on different aspects of (primarily viral) infections of human beings, farm animals, pets, zoo animals and wild animals. Other research interests are medical and veterinary medical entomology, viral infections transmitted by mosquitos and ticks, newly identified infection diseases and zoonoses. He served as local scientific organiser and member of the scientific committee of IMED 2018 and all six previous IMED conventions.

Multimodal pipelines yield sizeable prostate cancer data

Mapping the inflammatory landscape

Image analysis of prostate cancer is a challenging area for clinicians. The disease shows a low mutation burden compared to melanoma and stomach cancer, for example, making morpho-molecular correlation more difficult, and there is often very low inflammation.

Report: Mark Nicholls

With the role of tumour infiltrating lymphocytes (TILs) in prostate cancer currently unclear – and with the advent of new approaches to prostate cancer therapy, such as immunotherapy – the need to understand and map the inflammatory environment in prostate cancer is of increasing importance, according to urological pathologist Associate Professor Clare Verrill, at the University of Oxford.

In her presentation 'Image analysis in prostate cancer – mapping of the inflammatory landscape', Verrill outlined new research from her Oxford-based group at the Digital Pathology and AI Congress in London in December.

Verrill, who has a strong interest in digital pathology and image analysis and algorithm development, discussed a pipeline for mapping the inflammatory infiltrate in whole slide images of prostate cancer using the Visiopharm image analysis platform and determining associations with other pathological and outcome parameters. The professor reminded delegates of ongoing issues and difficulties with prostate cancer.

'We have a poor understanding of the natural history of prostate cancer and, as a consequence, we often over- and under-treat. There are not yet widely accepted and clinically relevant molecular groups,' she pointed out.

A high degree of heterogeneity

There is a high degree of heterogeneity and often very low inflammation in prostate cancer. A whole slide image of a tumour will contain around 100,000 lymphocytes, which would be extremely difficult for pathologists to quantify by visual assessment. Many previous studies on the effect of tumour infiltrating lymphocytes on outcome have used pathologists' assessments but, to quantify such large numbers of cells, image analysis is needed.

Previous literature is conflicting as to TILs and the effect on outcome in prostate cancer, Verrill added, but the literature is more consistent in other tumour types with high T-cell infiltration often associated with a better prognosis. 'The ultimate goal for us is to be able to predict the outcome and link morphological and molecular change' she said.

Shutterstock/Sebastian Kaulitzki

Prostate cancer remains the most common cancer in men with treatment options including radiotherapy, surgery, hormone therapy and focal therapies, although Verrill pointed to newer treatments of immune checkpoint blockade being tested. However, while they had worked well in other tumours, such as lung cancer, melanoma and renal cancer, in prostate cancer there had been a mixed response in clinical trials.

The Gleason grading system for prostate cancer dates from the 1960s and is the long-standing method of assessment.

Low inflammation in prostate cancer

With this in mind, Verrill's group endeavoured to look at integration of image analysis with next generation sequencing to update the assessment method.

'The inflammatory infiltrate of a tumour is often linked to the underlying genomics, for example, mismatch repair gene deficient colorectal cancer is characterised by dense inflammatory infiltrate,' said Verrill, who noted the frequent necessity to target oncogenic driver pathways combined with immunotherapy.

Previous prostate cancer research by others has shown loss of PTEN and immune suppression and loss or mutation of P53 and enhancement of the immunosuppressive microenvironment.

As prostate cancer infiltrates between benign glands, it is often difficult to find pure areas of tumour to sequence or conduct image analysis, but her team have developed an automated region of interest detection system using image analysis, which helps to overcome this. 'After region of interest detection, we quantified inflammatory markers using APPs (Application Protocol Packages), which were validated by manual counting,' Verrill explained.

From the image analysis pipeline, the team moved on to the sequencing pipeline and, for some cases, did whole exome sequencing.

'We have demonstrated the wealth of information that can be obtained by using novel multimodal pipelines,' Verrill concluded.

Clare Verrill is an Associate Professor in Pathology at the Nuffield Department of Surgical Sciences, University of Oxford and Honorary Consultant in Cellular Pathology with Oxford University Hospitals NHS Foundation Trust. Her research reflects a strong interest in digital pathology and includes projects on image analysis and algorithm development as well as urological research, such as helping to investigate novel molecular techniques for precision surgery.

Artificial intelligence could alleviate some pathology challenges

AI assists in PD-L1 scoring

A new deep learning algorithm, which demonstrates the potential of artificial intelligence (AI) to support pathologists, has been developed for PD-L1 scoring in tumour cells and immune cells in urothelial carcinoma samples, Mark Nicholls reports.

Speaking at the Digital Pathology and Artificial Intelligence Congress in London last December, Dr Michel Vandenberghe, from AstraZeneca, outlined how PD-L1 expression level assessment by pathologists can be used to help predict response to PD-L1/PD-1 targeted monotherapy.

With the new deep learning algorithm, developed as part of AstraZeneca's PostDoc programme, scientists there conducted experiments to establish whether AI can count the right cells in PD-L1 immunochemistry images and whether that information could provide some assistance to pathologists when assessing PD-L1 expression level.

AI, he said, has potential to add value to tissue-based companion diagnostics (CDx), assisting pathologists in their objective of biomarker expressions, particularly in ambiguous cases.

'AI could alleviate some challenges in pathology, such as interpathologist variability and the predicted shortage of pathologists,' Vandenberghe explained. 'AI has the potential to assist pathologists to assess biomarker expression reproducibly, to reduce diagnostic delays and to increase access to testing, as well as to leverage big data to improve patient selection.'

Noting how deep learning has been transformational in image analysis and has enabled AI to be at least as good as humans at performing certain visual tasks and, in some cases, to become better than humans, he cited examples where AI was demonstrated to accurately diagnose skin cancer from photographs and to detect lymph node metastasis in breast cancer tissue slide images.

The congress heard more detail about the development and analytical validation of a deep learning algorithm for automated scoring of PD-L1 expression in urothelial carcinoma samples processed with the VENTANA PD-L1 (SP263) Assay.

The approach that was implemented is based on an algorithm initially developed for interpretation of street scene images with applications for autonomous driving.

'That posed the question,' he explained, 'of whether the same deep learning model could be trained for a different application, such as to detect and classify cells in immunohistochemistry images.'

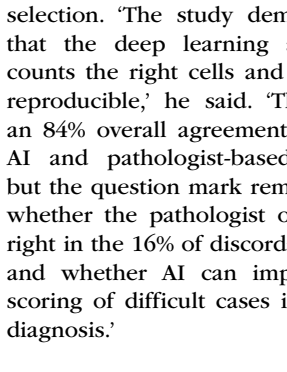
To train and evaluate the algorithm accuracy to count cells, the investigators manually annotated over 30,000 cells, which were used as ground-truth. 'There is good-to-excellent correlation between automated cell counting using the AI system and manual counting across all the defined cell types,' the scientist noted.

The algorithm was then scaled up to count cells in whole slide images (WSI) to assess whether a given tumour sample is PD-L1 High or PD-L1 Low/Negative.

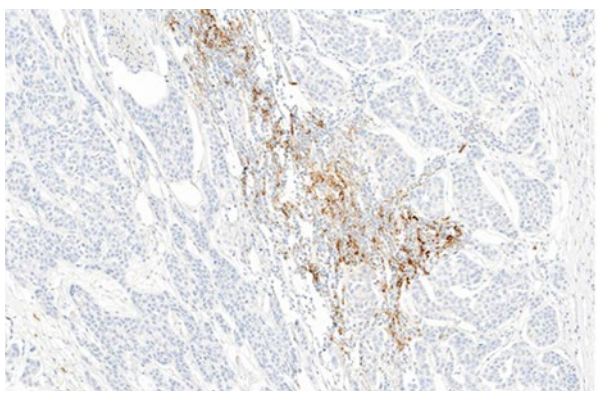
AstraZeneca then conducted experiments to assess the analytical performance of the deep learning algorithm and demonstrated high reproducibility and repeatability of the algorithm for PD-L1 scoring in tumour cells and in immune cells.

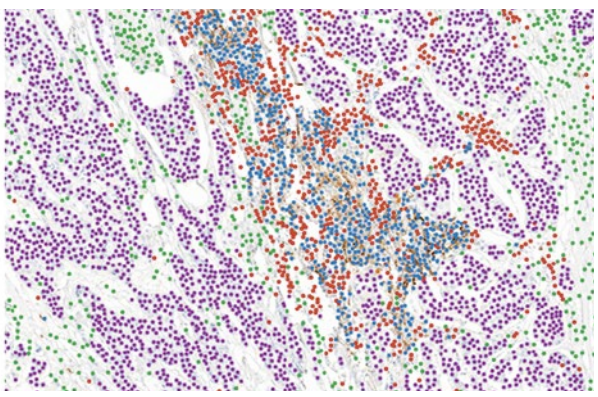
The last experiment looked at the correlation between the AI system and a pathologist, where there was a strong correlation between the pathologist and the AI system for scoring PD-L1 in tumour cells and a weaker correlation when scoring PD-L1 in immune cells.

Vandenberghe suggests the study contributes to building evidence for the use of deep learning to assist pathologists in the interpretation of PD-L1 expression for patient selection. 'The study demonstrates that the deep learning algorithm counts the right cells and is highly reproducible,' he said. 'There was an 84% overall agreement between AI and pathologist-based scoring but the question mark remains over whether the pathologist or AI was right in the 16% of discordant cases, and whether AI can improve the scoring of difficult cases in routine diagnosis.'



Michel Vandenberghe is Senior Scientist in the Precision Medicine Laboratories, Tissue Diagnostics, with AstraZeneca, and currently works on developing algorithms to analyse immunohistochemistry biomarkers.





From left: A slide stained for PD-L1 expression and the slide showing cells that were automatically detected using AI