

Medical Imaging for Improved Patient Care

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Foreword

The rapid development in medical research produces a continuous stream of new knowledge about disease processes, new therapeutic targets and the complex relationship between a person's genome and his/her related risk for disease. New technology is being developed for all aspects of patient care and the potential benefits of personalised medicine is gaining acceptance.

Medical imaging can now play a central role in the global healthcare system as it contributes to improved patient outcome and more cost-efficient healthcare in all major disease entities. More and better research in medical imaging is needed in Europe to increase our knowledge about disease processes and therapy management with the long-term goal of improving the health of European citizens.

The European Science Foundation's medical section, the European Medical Research Councils (EMRC) engaged in this science policy activity because medical imaging plays a role of ever-increasing importance at all levels of the healthcare system. EMRC assembled a group of European high-level experts in this field and conducted a Strategic Workshop in November 2006 to put a focus on research in the wide area of medical imaging, to analyse the *status quo* of medical imaging in Europe and to develop a policy for optimal use of research resources at the European level. Their recommendations are summarised in this policy briefing. To strengthen Europe's position in this truly global scientific field, emphasis has to be put on an increased collaboration, in particular between different universities, between imaging specialists and clinicians, between academia and industry, and between different imaging modalities. The establishment of interdisciplinary research groups of sufficient size provided with access to long-term funding is a prerequisite to fostering further development of this research area in Europe.

The aim of this science policy activity is to develop research-based knowledge on how to use medical imaging for the benefit of improved patient outcome, sustainable healthcare systems and increased competitiveness in the European medical industry.

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Introduction

Medical imaging is one of the fastest growing areas within medicine at present, both in the clinical setting in hospitals and in research and development (R&D).

Some important benefits from an increased research effort in medical imaging are expected in:

Improved Patient Care

- personalised medicine with individually tailored treatment
- more evidence-based decision making within healthcare
- less complications during and after surgery
- better understanding of the effect of treatments on diseases

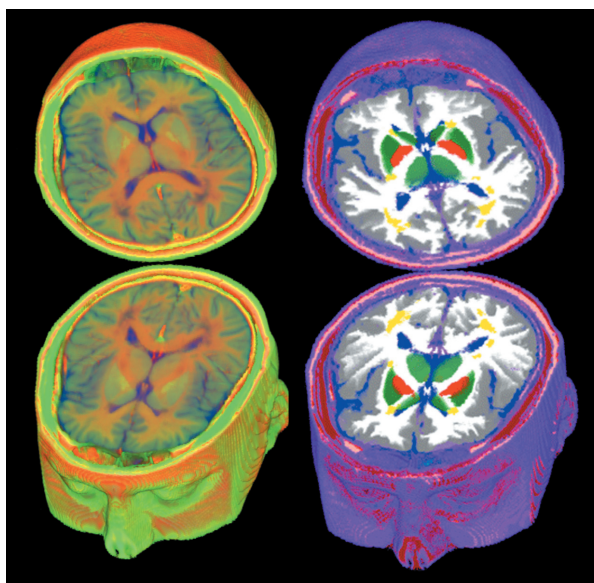


Figure 1: Multiparametric post-processing procedure and visualization of brain structures (left) and segmentation for tissue volume measurements (right) (courtesy of Prof. Bruno Alfano)

Improved Health of European Citizens

- screening of an entire population, e.g. for breast cancer, or targeted subpopulations with increased risk of specific disease entities
- better assessment of risk factors and better prevention of disease
- shorter time to cure for improved treatment efficacy
- less recurrence of disease
- decreased mortality and morbidity

Cost-Efficient Healthcare

- more rapid and accurate diagnosis
- less time to best choice of most efficient treatment
- quicker recovery after surgery
- shorter hospital stays
- cost-effective use of expensive diagnostic and surgical equipment

Socio-Economic Benefits

- less time out of work
- less need for long-term nursing

Improved Competitiveness of the European Medical Industry

- research-based development of new innovative technology and products
- focus on user-friendly equipment tailored for cost-efficient healthcare

Medical imaging has an important role in the care of all organ systems and disease entities, and better and increased medical imaging research may benefit the entire process of health and disease management, including:

- prevention
- individual risk assessment
- screening targeted subpopulations with increased risk of specific disease entities
- early detection of subclinical disease
- optimal choice of treatment based on personalised medicine
- image-guided minimally invasive surgery and interventions
- prognosis
- non-invasive monitoring of treatment effects for response-adjusted treatment in case of poor response
- patient follow-up to adjust multidrug therapy in chronic disease
- early detection of recurrence
- decision making tool for early-onset disease treatment and monitoring

Medical imaging covers many different imaging modalities: x-ray-based methods such as radiography and Computed Tomography (CT), Magnetic Resonance Imaging (MRI), ultrasound (US), nuclear medicine with Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT), and several methods in optical imaging. An important goal is to exploit the synergies of the different methods. This might be achieved in two ways:

- (1) correlative approaches, for example hybrid systems and image co-registration software (with image fusion of different modalities, such as PET and CT, MRI and PET, ultrasound and MRI).
- (2) standard disease-based protocols for diagnosis and follow-up.

Traditionally, medical imaging was a tool for non-invasive mapping of anatomy and for detection and localisation of a disease process. However, consecutive to a paradigm shift, it has been demonstrated that a wide variety of new medical imaging techniques and methods produce important biological information about physiology, organ function, biochemistry, metabolism, molecular biology and functional genomics. These new methods combine the ability to measure and quantify biological processes with the ability to localise the measured entities into a high-quality anatomical image. Further, advanced imaging techniques are now used for treatment instead of surgery: e.g. coronary angioplasty, treatment of aortic aneurysm and coiling of bleeding cerebral aneurysms. Exciting new advances in medical imaging are based on research in the areas of functional and molecular imaging and in the area of development of imaging biomarkers for improved prevention, diagnosis and treatment of disease.

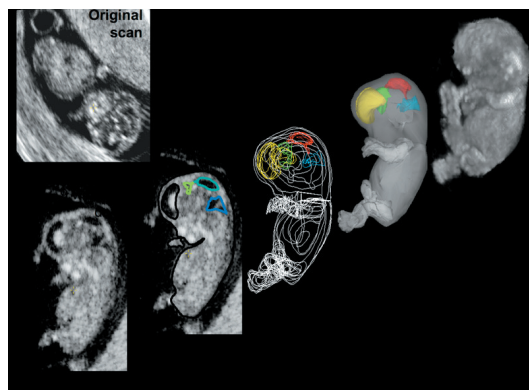


Figure 2: Ultrasound assessment of foetal growth and development of brain structures (courtesy of Prof. Sturla Eik-Nes)

The concept of personalised medicine is based on the potential for extensive mapping of the disease biology of an individual patient. Based on this information, treatment can be tailored to the individual patient's disease biology and genetic make-up. Medical imaging research has a crucial role to play in the development of better and more personalised medicine with the important benefits of being non-invasive and offering global anatomical coverage and co-localisation of the disease process and the relevant biological measurements.

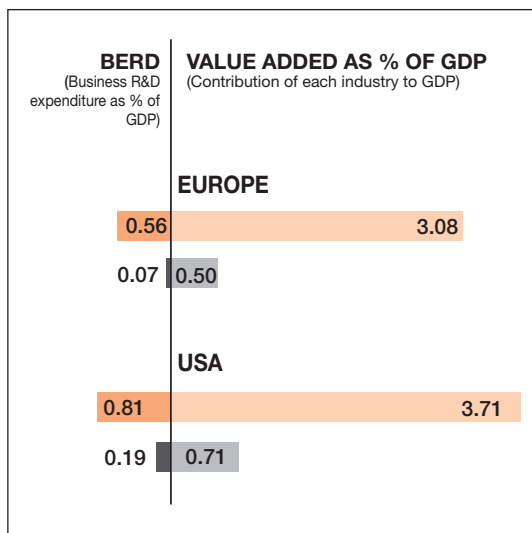
The important and exciting progress in biotechnology, nanomedicine and new innovative therapies is in many cases highly dependent on integration with medical imaging for successful application into standard clinical practice.

Examples are:

- guidance of biopsy sampling (by ultrasound, CT, MRI and PET) to obtain a relevant material for the *in vitro* mapping of the genetic expression and biology of the individual disease

- guidance of targeted drugs and of gene vector therapy and guidance of targeted radiation therapy
- guidance of stem cell therapy
- monitoring of cell differentiation and improved function in stem cell therapy

At present, medical imaging research in Europe is fragmented, and to a large extent financed by industry. As shown in the recent report "Key figures 2007 on Science, Technology and Innovation"¹, medical, precision and optical instruments is twice as R&D intensive and almost 50% bigger in the USA than in the EU (Figure 3). Therefore, an increased focus on research in this area is important for European competitiveness. The main goals should be increased public financing and improved cooperation at the European level.



Legend:
 ■ Total high-tech
 ■ Medical, precision and optical instruments

Source: DG Research
 Data: Eurostat, OECD, Groningen Growth and Development Centre
 Note: EUROPE does not include : BG, EE, LV, LT, LU, CY, MT, AT, PT, RO, SI, SK.

Figure 3: R&D expenditure for medical precision and optical instruments - EU27 compared to USA.

European Issues and Challenges

Collaboration, Interdisciplinarity, Pooling of Resources, Industry

For success in this research area it is necessary to create true multi- and interdisciplinary research environments where medical doctors, physiologists, physicists, chemists, mathematicians, molecular biologists, computer scientists and other technologists and technicians work closely together on the same research projects. These challenges are certainly not restricted to Europe and can only be overcome through long-term funding of large research projects. In most cases close collaboration between universities and major research centres is necessary to obtain the wide range of high-level competence, to achieve a research environment of sufficient size, and to obtain the necessary funding for infrastructure and large research projects.

A particular challenge is to achieve increased collaboration between imaging specialists (radiologists and nuclear medicine physicians) and the clinicians with knowledge of different organ systems and disease entities. The latter group also knows the special needs of imaging in relation to the disease areas they specialise in and the workflow in clinical departments.

Traditionally, medical imaging has been an activity where an imaging specialist makes an educated evaluation of the patient's disease, based on visual inspection of a limited number of images. However, we now see two emerging trends:

- an exponential increase in the number of images acquired for each patient
- the possibility of using the images as raw data for quantification in order to measure relevant entities in organ function, physiology and molecular biology

Medical imaging research must address these changes through focusing on Information and Communication Technology (ICT) solutions for decision support for radiologists, nuclear medicine physicians and other physicians, and also focusing on improved quantification of imaging results and biomarkers. The latter is also important for longitudinal follow-up of patients and comparability of results between centres in multicentre clinical trials.

Initiatives aimed at addressing the need for improved cooperation at the European level, such as the European Institute for Biomedical Imaging Research (EIBIR)², should be encouraged. However, it is of benefit to have a variety of different

¹ See report published 11 June 2007 at: http://www.eurosaire.prd.fr/7pc/doc/1182348125_kf_2007_prepub_en.pdf

² More at: <http://www.eibir.org/cms/website.php>

organisational structures to foster European collaboration of different types and at different levels, keeping in mind that they should be next to University Hospitals and Research Hospitals.

Furthermore, the EC ESFRI – European Strategy Forum on Research Infrastructures³ in the first European Roadmap for Research Infrastructures has put emphasis in the EATRIS⁴ proposal on the need for high performance facilities in medical imaging such as NeuroSpin for brain imaging.

Collaboration of academia with industry is important, both to attract funding and to ensure exploitation of R&D synergies. However, academia should take the lead in defining the research activities based on the dual goal of improved patient outcome and cost-efficient healthcare. In the long term, this approach will also benefit the competitiveness of the European medical imaging industry through a focus on R&D that addresses the patients' and clinicians' needs and encourages user-friendly equipment tailored for cost-efficient healthcare.

Translation of New Health Technology into New Clinical Practice

Translation of new technology into new clinical practice is a significant challenge. Acquisition of new technology within healthcare is often linked to marketing strategies of the industry and not based on extensive evaluation of which new methods may benefit patient care and which technologies have the potential for improving cost-efficiency in the healthcare system.

New methods in medical imaging are often adopted without sufficient scientific proof; and larger clinical trials with appropriate end-points to prove the benefits should be planned. Examples of relevant end-points are better choice of treatment and/or improved patient outcome due to information provided by new imaging techniques.

There are, however, some important challenges connected to the adoption of strict rules for evidence-based medicine in medical imaging. Improvements are often incremental with a more or less continuous process of technology improvement and new applications. And when there are cases of significant improvements, it has often been argued that the benefit of the technology is self-evident and that study designs with randomisation of patients to new and old technology is unethical. Industry should be requested to prove, prior to marketing, that new expensive technology is of added value to patient care. It is of importance for clinical research in general and for medical imaging research in particular that national existing regulations are adapted to allow:

- an easy organisation of good quality clinical research for the benefit of patients

³ More at: ftp://ftp.cordis.europa.eu/pub/esfri/docs/esfri-roadmap-report-26092006_en.pdf

⁴ EATRIS – European Advanced Translational Research Infrastructure in Medicine

- the protection of the individual patient who is included in a specific clinical study

Clinical imaging research is an area where Europe has taken on a leadership role that could be of benefit for the competitiveness of the European industry.

At the European level there is a need to develop, coordinate and adopt better systems for evidence-based medicine and health technology assessment for recommendations of standard practice in medical imaging.

For better translation into new clinical practice and widespread adoption of new advanced methods, it is necessary to establish two important tools at the European level:

- clinical practice standards for optimal use of medical imaging within each specific disease area
- education and training programmes tailored to both expert and non-expert users

Many imaging studies and most new methods in molecular imaging are based on the administration of molecular probes (contrast agents or tracers), currently managed as a generic pharmaceutical product by the regulatory bodies. An important limitation for translation into new clinical practice is the need for approval of the new drugs from the appropriate regulatory body, in particular for molecules administered in tracer amounts.

Two possibly conflicting trends are emerging for molecular imaging diagnostic applications:

- stricter rules for the approval of drugs and more expensive clinical trials
- more contrast agents and tracers tailored to specific use and/or small subpopulations of patients

There is the risk that many promising methods with huge potential benefit for improved patient outcome will never be translated into clinical practice because the potential market is too small to cover the costs of development.

Lack of Money and Resources as the Limiting Factor for Medical Progress

A challenge for the future healthcare system is that lack of money and resources may become the limiting factor for the services offered to the population. One reason is the demography arising from the ageing population. Another reason is the wide range of progress in medical research for diagnosis and treatment that is often costly. This challenge can only be met through the dual focus on improved patient outcome and cost-efficient solutions within healthcare systems.

Medical imaging may become an important contributor to obtain this dual goal. Even if new imaging technology is expensive it may contribute significantly to cost-efficiency in a labour-intensive healthcare system if the new methods lead to shorter hospital stays, less use of non-efficient treatment

(surgery, drugs and others), and less recurrence of disease. Improved patient outcome will also have an impact on the society through reductions in sick leave, disabilities and nursing expenses.

Cost-efficiency can also be obtained through development of advanced methods in medical imaging into user-friendly tools that can be applied also by non-expert users at the initial point of care.

Cost-efficiency for the healthcare system should be included as a separate end-point for imaging research, and researchers with competence in how to evaluate economic measures should be included in the planning of clinical trials.

Medical Imaging as a Research Tool

Medical imaging is an important research tool to obtain new knowledge about disease processes and treatment targets. Funding of medical imaging research and infrastructures is also needed for this purpose. Imaging is a non-invasive and well-suited technique for longitudinal studies that provides quantitative measures of the disease processes. Both in a preclinical and a clinical research setting there is medical imaging technology (equipment, contrast agents etc.) that will probably never be developed into tools for routine clinical use on patients, but which still benefit patient care through the new biomedical knowledge obtained.

Medical imaging also has an important role to play in the context of better and less expensive clinical trials for new drugs and therapies. Imaging may contribute in several ways:

- better inclusion/exclusion of patients
- better subgrouping of patients
- imaging biomarkers may be used as a surrogate outcome measure for the biological behaviour of different diseases

The importance of this is underlined by the acquisition of large imaging R&D centres by the pharmaceutical industry.

Safety Issues

The different imaging modalities present a wide spectre of potential hazards for the patients and for the environment. A well-defined problem is the ionizing radiation in the case of x-ray and nuclear medicine. There are also concerns about potential hazards from magnetic resonance when moving to higher fields and from ultrasound when moving to higher frequencies. Many of the advanced methods include injection of new molecular probes (contrast agents, tracers, nanopptides) with potential toxicity, side-effects and adverse events. Medical imaging research must also be focused on reducing these hazards and finding the best compromise between patient safety and potential benefits.

This safety assessment issue should be pro-actively addressed in collaboration between academies, health care industry and national and EC competent authorities.

Recommendations

The main recommendation is to:

1. Obtain more and better medical imaging research in Europe through:

- improved European collaboration, in particular between different universities, between imaging specialists and clinical doctors, and between different imaging modalities
- establishment of interdisciplinary research groups of sufficient size and with access to long-term funding
- improved collaboration between academia and industry where research goals are defined by academia

This is important in order to obtain medical imaging research with the necessary size and with true interdisciplinarity, and for research to be adequately focused on the dual goal of improved patient outcome and cost-efficient healthcare for the sake of improving European citizens' health, better societies in Europe and improved competitiveness of European medical industry.

Other important recommendations are to:

2. Obtain more evidence-based medicine at European level through:

- health technology evaluation
- validations of standard clinical practice for optimal use of imaging
- socio-economic measure of these new health technologies

3. Establish appropriate education/training for widespread translation of new technology into new clinical practice.

4. Develop advanced methods within medical imaging into user-friendly tools that can be applied also by non-expert users at the initial point of care.

5. Plan and fund both short- and long-term research activities:

- short-term applied research is necessary for translation of established new technology into new clinical practice
- long-term basic research is necessary to develop and evaluate new advanced methods, especially in the areas of functional and molecular imaging, and to use medical imaging as a research tool to obtain new knowledge about disease processes and new innovative therapies

Appendix

Some examples of promising new possibilities in medical imaging

To show the wide variety of the possible roles for medical imaging, a few examples of new, promising methods and applications are presented.

Example 1 (screening/risk factors/prevention)

Several imaging techniques are promising for the characterisation of atherosclerotic plaques. A main target is to establish imaging biomarkers for vulnerable plaques and to be able to find the patients that have increased risk of plaque-induced myocardial infarction and thrombo-embolic stroke. New imaging techniques and molecular imaging probes in PET, MRI and ultrasound may detect inflammatory and other biological processes in the plaques, and may be developed into a clinical tool for risk assessment of plaque vulnerability. Plaque imaging may also be developed into tools for monitoring the effect of preventive measures to reduce the plaque burden and/or the development into vulnerable plaques as shown in Figure 4. This may both show the effect of life-style measures as well as drug therapy.

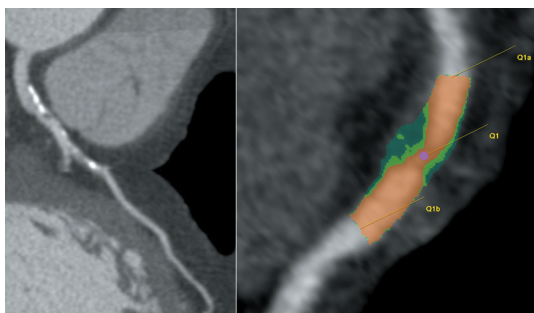


Figure 4: Coronary artery imaging with multidetector CT and post-processing characterisation of coronary plaques (courtesy of Prof. Gabriel P. Krestin)

Example 2 (early detection of subclinical disease)

There is exciting research activity with the combination of PET and functional MRI for the early diagnosis of neurodegenerative diseases, with a main focus on Alzheimer's disease. There are now PET tracers that are promising for non-invasive detection of Alzheimer plaques, and functional MRI may detect changes in functional brain activity. For an optimal strategy for halting and/or postponing the development of dementia using cognitive enhancing drugs, mental training and others, it is of great importance to detect the early changes in functional brain activity due to disease progression.

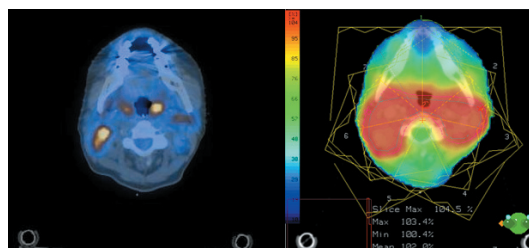


Figure 5: Radiation treatment planning (right) of head/neck cancer based on fusion of morphologic and functional information obtained with PET-CT (left) (courtesy of Prof. Liselotte Højgaard)

Example 3 (decision support for choice of treatment/personalised medicine)

CT, MRI and PET-guided images are used to target radiation therapy toward the cancer and avoid harmful radiation to healthy tissue (Figure 5).

Diagnostic imaging tests could be of great value in the selection of highly expensive treatment procedures: for example, new implantable pacemakers and arrhythmia defibrillators with great potential in the therapy of heart failure have high costs and only a certain subgroup of patients would benefit from this therapy. New imaging techniques such as advanced ultrasound techniques, imaging of cardiac innervation and metabolism may enable the identification of this subgroup of patients that will have an improved prognosis when using this expensive form of therapy.

Example 4 (theranostics)

Theranostics is a word to describe combined drug therapy and diagnostics⁵, and is the ultimate concept in targeted drug delivery. A molecule targeted for the disease tissue (e.g. cancer) is linked both to a nonactivated therapeutic drug and an imaging contrast agent (tracer). In the case of ultrasound, the drug may be encapsulated in a gas bubble and after injection the same ultrasound imaging equipment may be used first to ensure the correct localisation of the drug and then activate the drug through bursting of the bubble with ultrasound waves.

Example 5 (image guidance of stem cell therapy)

Image guidance may be applied to stem cell therapy on many levels. First guidance of the delivery and placement of the stem cells, then tracking of any migration of labelled stem cells, then monitoring of the cell differentiation for the target organ, and with functional imaging methods, monitoring of improved organ function. Imaging techniques that could be used for tracking stem cells in human include MRI, Nuclear Medicine (PET and SPECT) and possibly ultrasound.

⁵ See ESF Forward Look on Nanomedicine at : http://www.esf.org/fileadmin/be_user/research_areas/emrc/Nanomedicine.pdf

Example 6 (monitoring of drug therapy)

New imaging methods from PET and MRI produce biological information on the growth potential of malignant tumours. This may be applied to non-invasive monitoring of the treatment effects of cytostatic drug therapy (usually a combination of several drugs). FDG-PET⁶ can show a decrease in glucose uptake and different MRI methods can show reduction in angiogenetic potential. In a case of poor response, the treatment may be discontinued early on with a change to other drugs or to other therapeutic methods such as surgery or radiotherapy. Through this improved managed care the patient will get fewer adverse reactions, no ineffective therapy while it will lead to cost savings for the healthcare system.

Example 7 (image-guided surgery)

Imaging techniques can assist the surgeon both before and during surgery. Before surgery, image processing tools can provide realistic previews of the surgical field and of access pathways, with an interactive 3D anatomic display for appropriate planning.

During surgery, image guiding can be valuable for target localization and detection of boundaries allowing, for instance, more complete and accurate resection of tumours, limiting damage to normal tissues.

As an example, in neurosurgery it is important for the surgeon to avoid damage to the brain structures that will cause dramatic functional deficits (limb paralysis, language function, visual etc.). An integrated protocol of new MRI methods may, prior to the surgery, delineate important functional areas in the brain and their vital nerve fibre connections. This is of great help to the neurosurgeon in the planning of the operation, and can also be displayed for the neurosurgeon in the operating theatre and updated during the surgical intervention (tumour resection etc.), using image-guided minimal-invasive surgery with either MRI or ultrasound.

Ultimately, further development of robotic image-guided surgery will provide computer assisted tools to facilitate and increase safety of complex surgical procedures in all fields of surgery.

Example 8 (patient follow-up)

Cardiac ultrasound has reached a level where the myocardial wall function can be quantified and 3D visualised. Advanced ultrasound equipment is currently the size of a portable computer and with ongoing research it may reach the size of a cell phone. With further development in the user-friendliness of the advanced methods, it may be possible for patients using multidrug therapy in heart failure to have frequent follow-ups with an adjustment of dose, based on ultrasound image quantification of heart function, at the general practitioner's office.

Likewise as shown in Figure 6 below, combined morphofunctional imaging approaches (Doppler ultrasound and MRI with conventional and dedicated equipment) can be used for the staged detection of disease activities and for changes over time in rheumatic diseases, with potential beneficial effects for health expenditures.

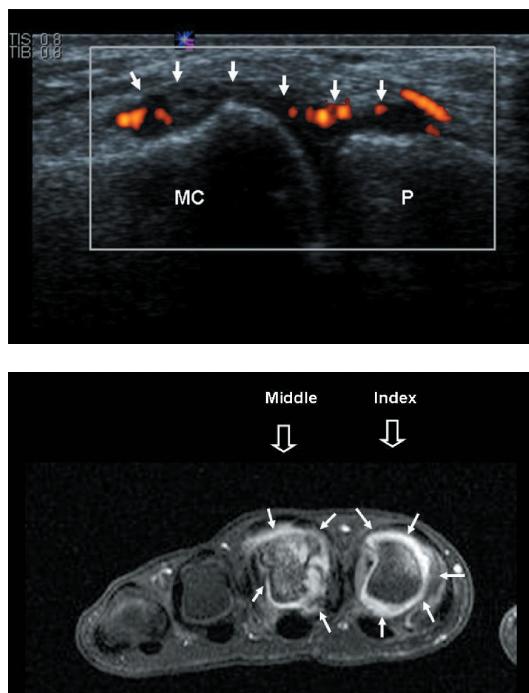


Figure 6: Doppler ultrasound image (top) of metacarpophalangeal joints showing active inflammation (synovitis). Corresponding MRI study (bottom) (courtesy of Prof. Paul Emery)

⁶ PET scanning with the tracer fluorine-18 (F-18) fluoro-deoxyglucose (FDG)

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