Insights Imaging (2011) 2:621–630
DOI 10.1007/s13244-011-0125-0

STATEMENT

Medical imaging in personalised medicine: a white paper of the research committee of the European Society of Radiology (ESR)

European Society of Radiology

Received: 4 August 2011 / Accepted: 4 August 2011 / Published online: 29 September 2011

Abstract The future of medicine lies in early diagnosis and individually tailored treatments, a concept that has been designated 'personalised medicine' (PM), i.e. delivering the right treatment to the right patient at the right time. However, the value of medical imaging in PM is frequently underestimated, as many policy makers forget the all-important *right location* in the PM paradigm. Medical imaging has always been personalised as it provides individual assessment of the location and extent of an abnormality, and in the future it will prove fundamental to almost all aspects of PM. Stratification based on imaging biomarkers can help identify individuals suited for preventive intervention and can improve disease staging. In vivo visualisation of locoregional physiological, biochemical and biological processes using molecular imaging can detect diseases in pre-symptomatic phases or facilitate individualised drug delivery. Furthermore, imaging is essential to patient-tailored therapy planning, therapy monitoring and follow-up of disease progression, as well as targeting non-invasive or minimally invasive treatments, especially with the rise of theranostics. For PM to reach its full potential, medical imaging must be an integral part. Radiologists need to be prepared for this new paradigm as it will mean changes in training, in research and in clinical practice.

Keywords Individualised medicine · Diagnostic imaging · Molecular imaging · Radiology · Medication therapy management

European Society of Radiology (ESR) (✉)
Neutorgasse 9/2,
1010 Vienna, Austria
e-mail: communications@myESR.org
URL: www.myESR.org

Introduction

'Personalised medicine' (PM) is increasingly becoming a hot topic in all areas related to biomedical research and has the potential to become the paradigm for clinical practice. The European Commission is dedicating a conference series to this topic [1]. The European Science Foundation (ESF) has initiated a 'Forward Look' campaign that should deliver "more precise medicine for the diagnosis, treatment and prevention of disease" for the European citizen [2]. Regulatory bodies such as the FDA [3] and EMA [4] have been challenged to find new approaches for registration of emerging PM technologies. National governments and public-private collaborations are funding large research programs and infrastructure dedicated to translation of basic PM concepts into clinical trials. Health-policy makers and insurance companies are in search of solutions for future implementation of PM strategies into daily care and reimbursement schemes.

Is PM a new concept, or is it only a new look at an old friend? Many clinicians would argue that they have always delivered care at the personal level and adapted their therapeutic approach to the individual needs of every patient. But is this really what we now regard as PM? Do modern emerging technologies in the era of molecular medicine allow completely new strategies? And what is the role of medical imaging in this paradigm which mainly focuses on different aspects of 'disease-omics'? Does medical imaging play a role in this new game?

Whatever PM is, radiologists and other imaging specialists have to be aware that PM is becoming and will remain the focus of interest in medical research and health-care policy in the coming years. Medical imaging, on the other hand, is still recognised as one of the motors of medical research and technology innovation, with unprecedented

practical achievements over the past 20–30 years. If imaging wants to maintain this leading role, it will have to define its precise position and contribution in this new field. However, many of the policy papers, programmes and funding schemes described above mention little or nothing about medical imaging nor about the benefits and contributions of imaging research to PM. Therefore the Research Committee (RC) of the ESR considers it of crucial strategic importance to define and describe how medical imaging benefits from and contributes to the overall conceptual framework of PM.

Definitions

According to Wikipedia, "personalized medicine is a medical model emphasizing in general the customization of healthcare, with all decisions and practices being tailored to individual patients in whatever ways possible. Recently, this has mainly involved the systematic use of genetic or other information about an individual patient to select or optimize that patient's preventative and therapeutic care" [5]. In other words, PM describes the concept of delivering the right treatment to the right patient at the right time. PM is facilitated by newly developed, powerful technologies allowing detection of "biological events at the molecular level, even before symptoms appear. The promise of personalised medicine is a future where disease is detected at the earliest possible time, and treatments are tailored to an individual patient's genetic profile" [6].

Sequencing of the human genome in 2003 opened the way to identify specific genes that are involved in particular diseases and thus to define genetic variants which either predispose a person to that disease or which regulate that person's sensitivity to a given treatment [2]. The concept of using these genetic differences to personalise healthcare has since taken over the perception of PM to such an extent that other means of personalising healthcare are being subsumed. However, except for a few monogenic diseases, proteins and other molecules (the 'omics' of that specific disease) have a more important influence on determining disease predisposition or therapeutic response than knowledge of the genetic sequence [2, 7]. Moreover, individual genetic differences have to be considered in the context of additional external variations—environment, diet, exercise, social circumstances—leading to variation in disease manifestation and drug activity [6].

The ESF expects that integration of several different 'omics' measurements will be needed to yield clinically useful biomarkers which can be used in tailoring treatment to an individual's physiological and biochemical profile [2]. Other terms used in the context of PM, such as integrated medicine, theranostics, pharmacodiagnostics and diagnostic/therapeutic partnering "address the use of detailed information about a patient's genotype or level of gene expression and a patient's clinical data [or biomarkers] to select medication, therapy or preventative measures that are particularly suited to that patient" [8]. Thus, one of the main aspects of PM will be to identify biomarkers able to characterise a cellular alteration leading to subclinical or manifest disease status as well as its specific reaction to various therapeutic attempts [9]. However, this approach again will lead to categorising or stratifying patients into smaller subgroups related to their risk or potential treatment profiles characterised by a combination of genetic, biochemical and even imaging biomarkers [10]. Such stratification can be further refined down to the level of an individual patient, and the term 'individualised medicine' could be more appropriate. Indeed, the National Library of Medicine has selected 'individualized medicine' as the Medical Subject Heading (MeSH) term for PM.

There are three main areas in which PM is expected to have a major health-management impact: in preventive medicine, in personalised diagnosis of disease and in therapeutic decisions targeting specific alterations. The *disease prevention* focus is on identifying—in an early pre-clinical stage—those subgroups of patients at risk of developing symptoms and signs of abnormal morphology and function. Such personalised prognostic stratification strategies may rely on genetic, environmental, social and other information. Identification of predictive biomarkers (biomolecular or imaging) can help to monitor disease development and preventive interventions. *Personalised diagnostics* implies the identification of the specific molecular substrate of alterations leading to disease. While most think of disease phenotype as answering the question: 'What is it?', an important part of personalised characterisation (and thus an integral part of PM) is location ('Where is it?') and extent ('What is involved?'). Furthermore, a complete diagnosis also needs information on the physiological characteristics of disease lesions (e.g. perfusion, flow, metabolism, diffusion). *Personalised treatment* focuses on the identification of patient subgroups likely to give a positive response to a given treatment [11], on the identification of subgroups of patients at risk of side effects during treatment [11], on monitoring of therapy response [11] and on individualised drug delivery systems allowing both real-time modulation of treatment approach and treatment delivery at a specific location. In other words, as Michael Berger so eloquently phrased it, "medical treatment tailored not just to symptoms, but to the biochemical profile of an individual's disease state (gene expression, proteome, dominant metabolic pathways, etc.)" [12].

Medical imaging in PM

In a critical description on the role of molecular imaging in PM, Adrian Nunn states: "For too long, it has been assumed that non-imagers understand the value of imaging not only from the research side, but also from the health care economics side. This has led to an underestimation of the value of imaging and, for molecular imaging, perhaps an idea that it is 'science' rather than high-value routine health care" [7]. Individual assessment of the location and extent of an abnormality is and always has been the basis of medical imaging, whether the 'abnormality' is a disease, a malformation or an injury. As such, medical imaging intrinsically enables PM. Examples of the unique and personalised information provided with imaging technologies are numerous: imaging allows localisation of disease and detection of the involvement of adjacent or more distant tissues and vital structures; imaging helps to plan and guide surgical or minimally invasive individualised therapies; and imaging enables assessment of the physiological environment and conditions of disease as well as prediction of the efficacy or possible side effects of treatment (assessing perfusion of lesions or diffusion in tissue as well as the vulnerability of adjacent organs).

In its 'Science policy briefing 28: medical imaging for improved patient care' [9], the ESF states that:

> Traditionally, medical imaging was a tool for non-invasive mapping of anatomy and for detection and localization 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.

PM will mean changes for radiology. According to Jim Thrall, "Imaging will play an increasingly important role in the assessment of therapeutic response, especially in cancer" [13] as this is an area in which variability among patients opens the door for individually tailored medications. According to a new market research report, interests from the imaging industry will drive PM in general and molecular medicine in particular [14]. Others recognise the threat which in vitro testing poses and maintain that we must rely on the unique ability of imaging to provide regional information, ideally including information on function, which cannot be replaced by ex vivo tests [7].

In her Presidential Address at the 2010 RSNA Annual Meeting, Hedvig Hricak, Chair of the Department of Radiology at Memorial Sloan-Kettering Cancer Center in New York, stated that medical imaging has become "a 'guiding hand' of personalized medicine for cancer care" [15]. Prof. Hricak names three categories in which imaging impacts PM: treatment decision-making, treatment planning and treatment follow-up. "Imaging provides essential road-maps for treatment planning" [15]. Hricak expects advances in techniques such as quantitative imaging and volumetric measurements to "change the landscape of clinical trials" [15]. Areas of opportunity for imaging in the era of PM include the following:

- Identification of predictive imaging biomarkers allowing both stratification of patient subgroups at risk of developing disease and monitoring of preventive measures
- Visualisation of cellular and molecular processes for early diagnosis of disease with the emerging discipline of molecular imaging
- Theranostics combining targeted imaging and targeted therapy enabling the identification of heterogeneous and localised response to therapy
- Treatment monitoring allowing early identification of treatment responders and non-responders
- Identification of localised pathophysiology (perfusion, diffusion, metabolism) of diseased tissue
- Individualised, image-guided drug delivery systems

However, implementing imaging-based PM strategies in clinical care is hampered by inadequate regulatory procedures. Both in Europe and in the U.S., new approval processes for PM approaches are needed [10]. This is a complex proposition given the mass of individual data and treatment options that arise from a PM approach, especially when imaging is involved. Adrian Nunn discusses both short- and long-term solutions: "In the short term, … ways [can] be explored to ease development and regulation of molecular imaging agents to foster development 'in spite of' the current framework. … The long-term approach [could be] to assess the feasibility and desirability of an alternative regulatory mechanism for molecular imaging agents" [7]. The FDA and EMEA must acknowledge the crucial role of medical imaging in PM in order to achieve durable policies for this field.

Medical imaging for personalised disease prevention

Biomedical imaging allows non-invasive or minimally invasive assessment of in vivo structural and functional changes that may reflect specific pathology. Recent developments in image data acquisition and analysis enable use of these techniques on a large scale. This makes it possible to investigate specific pathophysiological substrates of disease in a pre-symptomatic phase and at the population level. Population imaging is the large-scale application and analysis of medical images in controlled population cohorts. Population imaging focuses on finding imaging biomarkers that allow prediction and early diagnosis of diseases and preventive therapy.

Many common diseases are complex conditions caused by a large number of small, often additive effects arising from genetic predisposition, lifestyle and the environment. The development of new prevention strategies, leading to the promotion of health, requires access to and use of searchable repositories of biomedical data from population-based, prospective health surveys. These repositories include imaging data together with associated information about the individual subject. They have become indispensable for elucidating molecular processes and causal pathways, be they genetic or environmental, and for translating biomedical research into real improvements in healthcare (www.populationimaging.eu). Population imaging endeavors to find imaging biomarkers that can predict later development of disease, either on their own or by supplementing established risk factors. Clinical phenotyping and correlation with genome-wide analysis aid the search for genetic mutations predisposing one to a specific disease by "aggregating subjects into groups with higher probabilities of having common genotypes" [13]. Some even believe that successful identification of prognostic biomarkers will reduce the number of surgeries [2]. Several projects performed in healthy populations have already shown that imaging has benefits for the determination of disease predictors and can enable the stratification of a healthy population into different risk categories. Imaging may become the key to identifying people that could benefit from preventive intervention (Fig. 1).

Prof. Dr. Olga Golubnitschaja—Secretary-General of the European Association for Predictive, Preventive and Personalised Medicine (EPMA)—summarised the situation well in her landmark book *Predictive Diagnostics and Personalized Treatment: Dream or Reality* [16]:

> Essential components of [predictive, preventive and personalized medicine] include well-organized population screening protocols utilizing novel diagnostic biomarkers of disease states, targeted prevention of common human pathologies, optimal treatment planning and personalized medicine thereby resulting in substantial improvement of the quality of life. This approach also offers the advantage of delivering care at potentially reduced costs to the population at large thereby addressing social and ethical issues related to access to and affordability of health care.

The flip side of the preventive medicine coin involves *incidental findings* and *overdiagnosis*. In a cohort of subjects undergoing a CT angiography of the abdominal aorta and the lower extremities, 15% of patients had incidental findings of potential clinical relevance [17], and similar rates have been reported in healthy subjects undergoing cranial MRI for research purposes [18]. When an asymptomatic disease is diagnosed (either by screening or as an incidental finding), we have the potential for overdiagnosis. Overdiagnosis is the diagnosis of irrelevant diseases, diseases which are so stable or indolent that they would not have become clinically relevant during the subject's life. Overdiagnosis leads to unneeded treatment with potentially harmful side effects and thus causes both economic and emotional burden. The magnitude of overdiagnosis has been recently estimated to be as much as 25% of mammographically detected breast cancers, 50% of chest x-ray and/or sputum-detected lung cancers, and 60% of prostate-specific antigen-detected prostate cancers [19]. The challenge for PM is to recognise when the burdens of treatment outweigh the benefits for a given patient, taking into account the individual characteristics of the subject, including his or her personal values and preferences.

Medical imaging for personalised diagnosis

In classical diagnostic imaging, information is primarily derived from differences in how various tissues intrinsically respond to the imaging modality or the compartmentalisation of simple contrast agents, thus showing morphology. While classical macroscopic imaging provides some of the most important 'individualised' information on many diseases—namely their localisation and extent—its value for determining the specific aetiology is sometimes limited. Final diagnosis within an acceptable degree of uncertainty is usually possible based on a combination of clinical, biochemical and imaging information (Fig. 2). However, establishing the cellular, molecular, or genetic pathways leading to disease requires microscopic, metabolic and/or functional information. Such information can be obtained by ex vivo analysis of tissue, and image-guided tissue sampling provides the means to target and investigate specific areas of the lesions.

Molecular imaging is a new, in vivo approach which is likely to replace several aspects of ex vivo tissue analysis and which will be key in realising PM. Molecular imaging

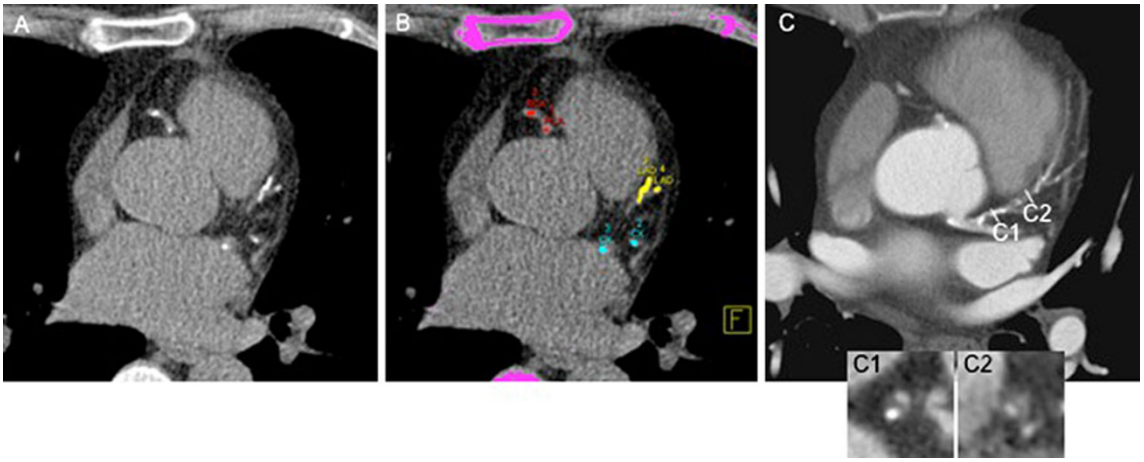

Fig. 1 Imaging to identify beneficiaries of preventive medicine. Elevated calcium score with associated chronic total occlusion of the left anterior descending coronary artery (LAD) in a 79-year-old male. **a** Axial unenhanced image shows calcifications in the LAD, in the circumflex (CX) coronary artery and in the right coronary artery (RCA). **b** The calcifications in the three coronary arteries are *colour coded* by the automated calcium detection algorithm. The total Agatston calcium score in this patient was 637, suggesting increased risk for a coronary event. **c** CT coronary angiography demonstrates an obstructive coronary stenosis due a mixed plaque in the proximal LAD (*C1*) and a chronic total occlusion in the mid LAD (*C2*)

can be used to detect diseases much earlier, visualise biological processes at the cellular and molecular level in living organisms and determine changes in local biochemistry [12]. Multiple methods and biomarkers have now been described for imaging the temporal and spatial biodistribution of a molecular probe as well as related biological processes such as cell proliferation, apoptosis, angiogenesis, hypoxia and gene activation and expression [20]. These molecular imaging techniques can lead to enhanced, individualised clinical management of diseased patients at an early stage. For instance, 'reporter genes' which are part of a gene therapy can be used to determine if transfection was successful and to monitor gene activity and distribution in the individual patient [13]. Molecular imaging is intrinsically different from the large, in vitro genomic or proteomic arrays currently popular. Such arrays survey a large number of genes or proteins, while molecular imaging concentrates on just one or two proteins. However, the "apparent reduction in utility, because of the smaller number of analytes, is more than compensated by the regional and dynamic information [molecular imaging] provides" [7].

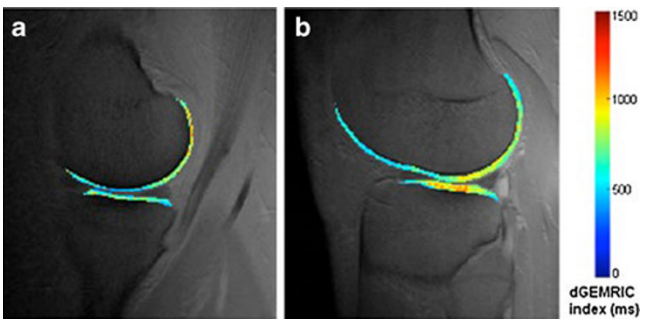

Fig. 2a, b Novel imaging techniques contribute to personalised diagnosis. Delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) in a patient with complaints of early knee osteoarthritis (**a**) and a patient without knee complaints (**b**). With dGEMRIC it is possible to quantitatively assess cartilage quality before the onset of morphological changes, by measuring its glycosaminoglycan content. In patient **a**, decreased dGEMRIC index is shown particularly in the weight-bearing cartilage of the femoral condyle and tibial plateau compared to patient **b**. This indicates reduced glycosaminoglycan content, and hence reduced cartilage quality, in the early osteoarthritic knee. Novel quantitative radiological techniques such as dGEMRIC may aid in personalised therapeutic decision-making in early stage osteoarthritis because patients who are likely to benefit from therapeutic interventions can be identified more accurately

A major area where diagnostic imaging techniques have been used extensively is disease staging. Staging, or in other words the description of disease extent (and implicitly severity), has an immediate and important impact on choice of therapeutic options and on personalised prognostic stratification. Methods commonly used for staging are those that combine fast whole-body coverage with high sensitivity for disease detection. The whole-body approach and sensitivity of diffusion-weighted MRI and PET-CT are useful in disease staging, allowing assessment of the disease status of a patient and selection of the most appropriate treatment approach for that patient from a single examination [21, 22]. Staging and stage migration using different cross-sectional imaging techniques such as CT, MRI or PET help avoid futile operations, resulting in improved personalised treatment and reduced patient morbidity. Similarly, precise delineation of primary and metastatic lesions helps to optimise target volume definition

in radiation therapy [22], and knowledge about functional use of brain tracts can aid in optimal surgical planning for tumours of the brain [23]. Clearly, novel macroscopic and molecular imaging techniques will form the cornerstone of personalised diagnosis in the near future.

Medical imaging for personalised therapy

Medical imaging contributes to therapeutic PM in several key areas. The role of medical imaging in personal, patient-tailored therapy planning, therapy monitoring and follow-up of disease progression is obvious to most medical professionals, but medical imaging also contributes to personalised therapy via image guidance of minimally invasive interventions as well as targeting of non-invasive focused ultrasound or radiation treatments.

In many diseases 'one size fits all' no longer applies. The application of medical imaging is changing treatment management to a tailored approach, with both health and economic benefits. Treatment monitoring helps avoid both unnecessary drug toxicities and ineffective treatments, with resultant reduction in healthcare costs [21]. Molecular imaging not only allows detection of disease in very early or even pre-clinical stages but also helps to determine subsequent personalised therapies. It may be also used for prognostic classification and for the choice of personalised follow-up strategies [21]. Furthermore, "molecular imaging may provide unique means for the selection of patients who may benefit from targeted therapies, as well as [allowing] monitoring of early responses to treatment and [enabling] subsequent restaging" [20]. Image-guidance of biopsy sampling (by US or CT) helps to obtain relevant material for the in vitro mapping of the genetic expression and biology of the individual disease, while metabolic imaging using PET-CT is useful for selecting cancer patients who are likely to respond to specific radiopeptide treatments and this examination can also be used as a baseline for response monitoring [22]. Therapeutic applications of imaging within PM can be categorised into four areas: drug discovery, theranostics, image-guided interventions and drug delivery, and therapy monitoring.

Drug discovery

Imaging is establishing itself as a vital part of pharmacological research, where it can be used to identify and evaluate novel target moieties. Indeed, in its Critical Path Initiative, the U.S. Food and Drug Administration (FDA) has recognised the new role of medical imaging in drug development and regulatory approval [24]. Although the Initiative emphasises the role of imaging in assessment of biomarkers, medical imaging also has other applications in drug discovery: "a molecular imaging probe can be used to determine target occupancy before and after administration of a new drug candidate, which helps to assess binding affinity and to determine correct dosages" [13].

Very important is the rise of (imaging) biomarkers as surrogate endpoints for clinical trials. Biomarkers that indicate response to therapy may be the same as those used for diagnosis or characterisation, but do not have to be. Given that validated surrogate endpoints allow dramatic shortening of clinical trials, with associated savings and a faster availability of new treatments, this is an area in which both the pharmaceutical industry and the healthcare authorities are pushing for biomarker use. Molecular imaging and radiopharmaceuticals are particularly important within this context as they allow in vivo visualisation of the effect of the treatment. Indeed, Adrian Nunn feels that the "interest in imaging agents generated by the Critical Path Initiative probably means that all new imaging agents—molecular or morphologic, existing technologies or new technologies—will be seen in a new light" [7].

Theranostics

According to Wikipedia, theranostics is "the term used to describe the proposed process of diagnostic therapy for individual patients—to test them for possible reaction to taking a new medication and to tailor a treatment for them based on the test results" [25]. Theranostics are inextricably linked to PM as they are individualised products providing both diagnosis and treatment. The most common example of a theranostic is targeted radionuclide therapy. Targeted radionuclide therapy combines "the favorable targeting properties of peptides and antibodies with the effectiveness of radiation-induced cell death. A major advantage … is the possibility to determine the selective accumulation in the targeted tissue by molecular imaging studies … using structurally identical diagnostic compounds" [20]. Depending on the exact radionuclide used, theranostics provide both a unique signature for imaging the biodistribution of the target moiety (diagnosis and monitoring) and micro-environmental radiotherapy (treatment) and permit one to predict the biodistribution of radiation dose, stage the tumour and individually monitor the efficacy of treatment with the same basic compound that is being used to target and treat the disease [20]. "This novel class of pharmaceuticals offers the potential to develop patient-specific therapies based on the new 'image and treat' approach" [20].

Alternatively, different biomarkers can be combined to characterise the diseased tissue [21]. These "visible" pharmaceuticals have enormous potential in PM.

The evolving era of nanotechnology will further boost the development and use of theranostics. New materials and techniques are facilitating the production of various nano-

particles suitable both as (targeted) imaging probe and drug carrier. Currently various types of nanoparticles are being investigated as versatile tools for theranostics purposes [26, 27]. A major advantage of nanoparticles for theranostics would be the high payload of both therapeutic agent and imaging probe that can be delivered to the target tissue. Specific examples of theranostic agents currently under investigation include liposomal vesicle formulations containing cytostatic drugs and MR contrast agents [28, 29], carbon nanotubes as multifunctional carriers for radioisotopes for treatment and imaging [30], and dendriworms for efficient delivery of siRNA (small interfering RNA) visualised by optical imaging or MRI [31]. An additional new approach in theranostic strategies is 'cellular theranostics'. In this approach, cells would be used for diagnostic as well as therapeutic purposes [32, 33].

Image-guided interventions and drug delivery

Image-guided interventions provide the means to deliver therapies locally at the disease site, whether the therapies are based on chemical compounds (including drugs and radiotherapeutics), genes, devices (including stents), cells, sound waves (HIFU) or temperature fluctuations (hyper- and hypothermia). Most current interventional image-guided procedures are individually tailored to the local anatomic and functional circumstances as well as the personal needs of the patient. In this way, image-guided interventions are in themselves an important and integral part of PM.

Medical imaging also plays an important role in individualised drug delivery, by providing information about the locoregional physiological conditions ('regional proteomics' [7]) important for drug targeting [10], by triggering nanotechnological carriers to release active drug [10] or by monitoring differentiation of stem cell–based therapeutics [9]. Although the past 30 years of drug delivery research have focused on targeting carriers such as liposomes, polymeric nanoparticles and micelles to the disease site, new developments promote the selective release of bioactive compound after application of a trigger [10]. The trigger mechanism can be applied locally and at specific times, depending on the individual patient's needs, and can be selectively applied with interventional techniques such as high intensity focused ultrasound (HIFU) under the guidance of MRI [10]. "[HIFU] is the only clinically viable technology that can be used to achieve a local temperature increase deep inside the human body in a non-invasive way. … MRI can be used to provide continuous temperature mapping during HIFU for spatial and temporal control of the heating procedure and prediction of the final lesion based on the received thermal dose" [34]. Other molecular imaging–based approaches for PM are also invading the field of image-guided interventions, including approaches involving gene expression, drug activation and drug delivery. These types of techniques can be further combined with specially designed contrast agents or drug delivery systems to achieve even more personalised approaches.

Therapy monitoring

Therapy monitoring is an area which PM is expected to dominate within a few years. Current monitoring is based mainly on anatomical imaging—frequently still assessed on 2D images (e.g. according to the RECIST criteria). This field is a paradigmatic example of the gap between current practice and advances in technological imaging. However, the new RECIST 1.1 criteria [35] have expanded to include lymph node evaluation and the use of PET.

New approaches using molecular imaging will document changes in local biochemistry or physiology as well as anatomy, which should provide even earlier differentiation between responders and non-responders. The simplest version of this is ^{18}F-fluorodeoxyglucose (^{18}FDG) imaging (Fig. 3), which assesses the glucose uptake and thus the metabolic activity level of various cancers [7], but more specific probes can and are being developed for individual types of cancer [36]. "One can foresee the further expansion of PET imaging–based personalised management of cancer, which, based on the strong evidence generated through a number of clinical studies and by its ability to monitor disease activity at the individual level, is likely to be increasingly integrated into the standard evidence-based clinical practice of oncology" [22].

There is one problem with monitoring approaches based on a single marker, a problem which has plagued physicians in oncology and related fields for decades: the heterogeneity of tumours. While tumour heterogeneity also explains individual variations in treatment response, a monitoring approach based only on a single marker is sensitive to variations in expression of that marker. "This defines the weakness of serum analyses, which provide an average signal of output from all lesions, or of a biopsy program to characterize a tumor—if all can be different, then all must be characterized" [7]. Signal localisation and regional differences are the strength of imaging. Thus, "imaging biomarkers may be used as a surrogate outcome measure for the biological behaviour of different diseases" [9].

However, molecular imaging approaches based on a single probe may be insufficient, especially as alternative pathways may replace the function of the targeted pathway [7, 8], resulting in a false negative test outcome. This seeming weakness, however, can actually be a strength—by combining imaging markers from different pathways, it may be possible to assess the type of physiological escape

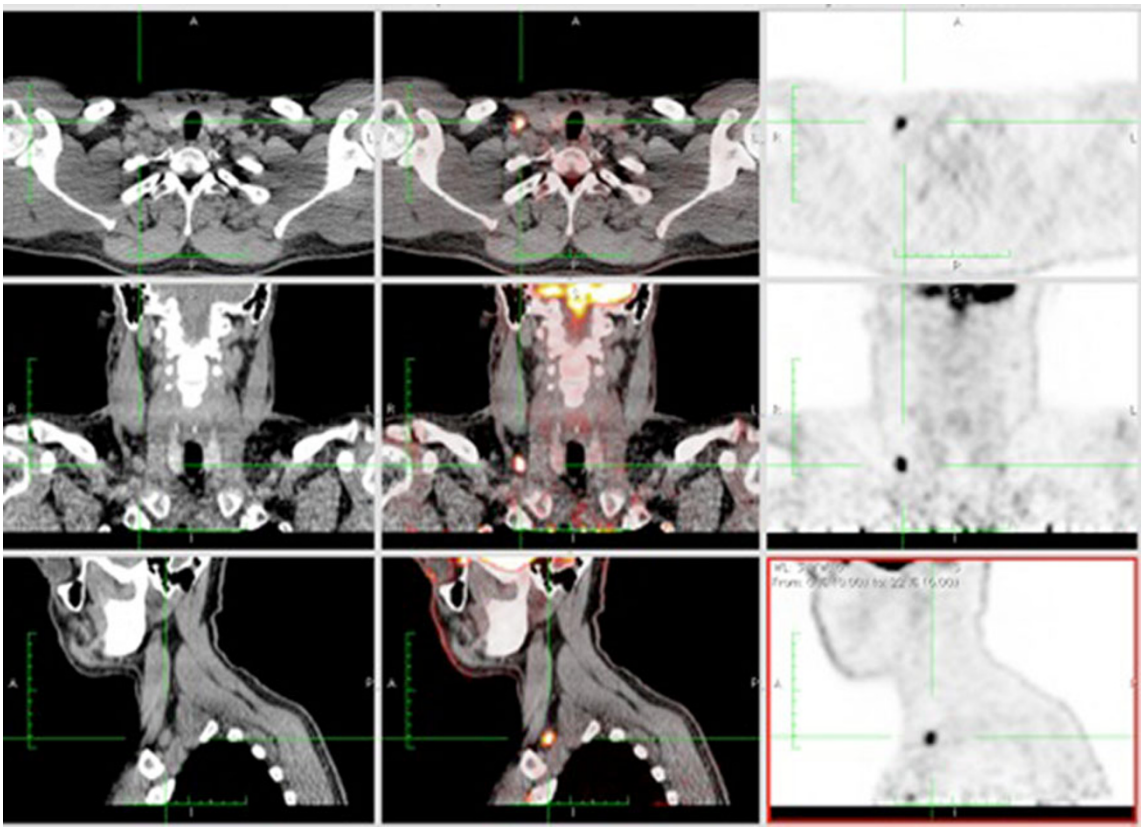

Fig. 3 ^{18}FDG imaging to monitor cancer treatment. Computed tomography (CT, *left*), ^{18}FDG positron emission tomography (PET, *right*) and PET/CT fusion (*middle*) images in a patient with Hodgkin's lymphoma, evaluated after eight courses of chemotherapy. Intense hypermetabolism on FDG-PET corresponds with localisation on CT in a small right supraclavicular lymph node, clearly indicating recurrent lymphoma. (Figure courtesy of Dr. Roelf Valkema, Department of Nuclear Medicine, Erasmus MC)

mechanisms of a tumour (or other disease) as well as tumour presence [8], enabling individual treatment to be fitted in real time to the type of response, which is of course PM in its most basic sense. However, a real concern when using expensive molecular imaging agents is cost-effectiveness—"to demonstrate that the increased cost of the imaging provides a commensurate increase in value" [7].

Conclusions

While Jim Thrall's 2004 statement that "each individual is now an '*n*' of one" [13] was certainly premature, the essence is correct: PM will probably take over medical care in the near future. However, many reports on PM fail to recognise the important role that medical imaging must play in a PM approach.

In the not all too distant future, each patient will expect completely individualised prediction, diagnosis and treatment. Radiologists need to be prepared for this new paradigm as it will mean changes in training (PM should be included in post-graduate education), in research (e.g. with a stronger role of radiologists in pharmacological research) and in clinical practice (taking into account the whole profile of the patient, including genetics, risk factors and personal values and preferences). In order to adapt medical care to the individual situation, knowledge is needed, not only about the biochemical and physiological characteristics of the individual's disease, but also about location, extent and inter- and intra-lesion heterogeneity. To gain this knowledge, biomarkers of different types will need to be combined. Genomics- and proteomics-based biomarkers are imperative, as are imaging-based biomarkers.

The 'three R's' of PM are right treatment, right time, right location. Medical imaging is essential for excellent PM as it is the only patient-friendly means to obtain information on location, especially with regard to heterogeneous expression within an individual patient. However, medical imaging can also contribute important information regarding expression patterns, perfusion, metabolic activity etc., which can be pivotal in deciding what the best treatment is, and when is the best time to give it.

Furthermore, medical imaging plays a critical role in all aspects of PM: prediction, diagnosis and especially treatment. For PM to reach its highest potential, medical imaging must be an integral part.

Acknowledgements This article was kindly prepared by the Working Group (Chair and lead/corresponding author: Gabriel P. Krestin, Members: Bernard van Beers, Roberto Blanco, Charles Cuenod, Thomas Helbich, Paul Parizel, Francesco Sardanelli) of the ESR Research Committee (Chairman: Luis Martí-Bonmatí, Members: Bernard van Beers, Guy Frija, Vicky Goh, Nicolas Grenier, Thomas Helmberger, Juergen Hennig, Juerg Hodler, Fabian Kiessling, Gabriel P. Krestin, Celsos Matos, András Palkó, Siegfried Trattnig) on behalf of the European Society of Radiology (ESR). It was approved by the ESR Executive Council in June 2011.

References

1. European Commission (2011) European perspectives in personalised medicine. http://ec.europa.eu/research/health/events-06_en.html. Accessed 23 May 2011
2. European Science Foundation (2011) Personalised medicine for the European citizen—towards more precise medicine for the diagnosis, treatment and prevention of disease. http://www.esf.org/activities/forward-looks/medical-sciences-emrc/current-forward-looks-in-medical-sciences/personalised-medicine-for-the-european-citizen/more-information.html. Accessed 23 May 2011
3. Hamburg MA, Collins FS (2010) The path to personalized medicine. N Engl J Med 363:301–304. doi:10.1056/NEJMp1006304
4. Abadie E (2011) Personalised medicine and use of biomarkers in drug development: an EU regulatory perspective. http://ebookbrowse.com/eu-regulatory-personalised-medicine-ema-pdf-d109827768. Accessed 25 April 2011
5. Wikipedia (2011) Personalised medicine. http://en.wikipedia.org/wiki/Personalised_medicine. Accessed 25 April 2011
6. Society of Nuclear Medicine – Center for Molecular Imaging Innovation and Translation (2011) Providing personalized medicine with molecular imaging. http://www.molecularimagingcenter.org/index.cfm?PageID=6370. Accessed 11 April 2011
7. Nunn AD (2007) Molecular imaging and personalized medicine: an uncertain future. Cancer Biother Radiopharm 22:722–739. doi:10.1089/cbr.2007.0417
8. Eckelman WC et al (2008) Targeted imaging: an important biomarker for understanding disease progression in the era of personalized medicine. Drug Discov Today 13:748–759. doi:10.1016/j.drudis.2008.05.009
9. European Science Foundation (2007) Science policy briefing 28: medical imaging for improved patient care. http://www.esf.org/fileadmin/links/EMRC/ESF_POLICY28_V09_HD.pdf. Accessed 23 May 2011
10. Crommelin DJ et al (2011) 'Personalized medicine' through 'personalized medicines': time to integrate advanced, non-invasive imaging approaches and smart drug delivery systems. Int J Pharm 415:5–8. doi:10.1016/j.ijpharm.2011.02.010
11. Pene F et al (2009) Toward theragnostics. Crit Care Med 37(1 Suppl):S50–S58. doi:10.1097/CCM.0b013e3181921349
12. Berger M (2006) Molecular imaging as a step towards personalized medicine. http://www.nanowerk.com/spotlight/spotid=1001.php. Accessed 23 May 2011
13. Thrall JH (2004) Personalised medicine. Radiology 231:613–616. doi:10.1148/radiol.2313040323
14. Medical News Today (2009) Imaging crucial for "personalized medicine" to succeed, says report. http://www.medicalnewstoday.com/articles/168524.php. Accessed 11 April 2011
15. Hricak H (2011) Oncologic imaging: a guiding hand of personalized cancer care. Radiology 259:633–640. doi:10.1148/radiol.11110252
16. Golubnitschaja O (2009) Predictive diagnostics and personalised treatment: dream or reality. Nova Science, New York
17. Naidu SG et al (2010) Incidence of highly important extravascular findings detected on CT angiography of the abdominal aorta and the lower extremities. Am J Roentgenol 194:1630–1634. doi:10.2214/AJR.09.3538
18. Hartwigsen G et al (2010) Incidental findings are frequent in young healthy individuals undergoing magnetic resonance imaging in brain research imaging studies: a prospective single-center study. J Comput Assist Tomogr 34:596–600. doi:10.1097/RCT.0b013e3181d9c2bb
19. Welch HG, Black WC (2010) Overdiagnosis in cancer. J Natl Cancer Inst 102:605–613. doi:10.1093/jnci/djq099
20. Bouchelouche K, Capala J (2010) 'Image and treat': an individualized approach to urological tumors. Curr Opin Oncol 22:274–280. doi:10.1097/CCO.0b013e3283373d5c
21. Society of Nuclear Medicine (2010) Personalized medicine: molecular imaging predicts treatment success in many cancers. http://www.physorg.com/news202557856.htm. Accessed 11 April 2011
22. Basu S (2010) Personalized versus evidence-based medicine with PET-based imaging. Nat Rev Clin Oncol 7:665–668. doi:10.1038/nrclinonc.2010.121
23. Smits M et al (2007) Incorporating functional MR imaging into diffusion tensor tractography in the preoperative assessment of the corticospinal tract in patients with brain tumors. Am J Neuroradiol 28:1354–1361. doi:10.3174/ajnr.A0538
24. US Food and Drug Administration (2009) Medical imaging and drug development. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm092895.htm. Accessed 31 May 2011
25. Wikipedia (2011) Theranostics. http://en.wikipedia.org/wiki/Theranostics. Accessed 28 April 2011
26. Janib SM et al (2010) Imaging and drug delivery using theranostic nanoparticles. Adv Drug Deliv Rev 62:1052–1063. doi:10.1016/j.addr.2010.08.004
27. Xie J et al (2010) Nanoparticle-based theranostic agents. Adv Drug Deliv Rev 62:1064–1079. doi:10.1016/j.addr.2010.07.009
28. Kim MJ et al (2011) Preparation, characterization, cytotoxicity and drug release behavior of liposome-enveloped paclitaxel/Fe3O4 nanoparticles. J Nanosci Nanotechnol 11:889–893. doi:10.1166/jnn.2011.3267
29. Kono K et al (2011) Multi-functional liposomes having temperature-triggered release and magnetic resonance imaging for tumor-specific chemotherapy. Biomaterials 32:1387–1395. doi:10.1016/j.biomaterials.2010.10.050
30. Hong SY et al (2010) Filled and glycosylated carbon nanotubes for in vivo radioemitter localization and imaging. Nat Mater 9:485–490. doi:10.1038/nmat2766
31. Agrawal A et al (2009) Functional delivery of siRNA in mice using dendriworms. ACS Nano 3:2495–2504. doi:10.1021/nn900201e
32. Arbab AS et al (2010) Differentiation of glioma and radiation injury in rats using in vitro produce magnetically labeled cytotoxic T-cells and MRI. PLoS One 5:e9365. doi:10.1371/journal.pone.0009365
33. Panagiotou T, Fisher RJ (2011) Enhanced transport capabilities via nanotechnologies: impacting bioefficacy, controlled release strat-

egies, and novel chaperones. J Drug Deliv 2011:902403. doi:10.1155/2011/902403
34. Moonen CT (2007) Spatio-temporal control of gene expression and cancer treatment using magnetic resonance imaging-guided focused ultrasound. Clin Cancer Res 13:3482–3489. doi:10.1158/1078-0432.CCR-07-0204
35. Eisenhauer EA et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228_247. doi:10.1016/j.ejca.2008.10.026
36. Kwekkeboom DJ et al (2010) Somatostatin-receptor-based imaging and therapy of gastroenteropancreatic neuroendocrine tumors. Endocr Relat Cancer 17:R53–R73. doi:10.1677/ERC-09-0078