PET and the role of *in vivo* molecular imaging in personalized medicine

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In order for personalized medicine to become a clinical reality a number of hurdles, both technological and regulatory in nature, need to be addressed. Our ability to image biological and pathological processes at a molecular level using positron emission tomography (PET) imaging offers an unparalleled opportunity to radically reform the manner in which a disease is diagnosed and managed. The degree to which current innovations in PET science will translate into clinical practice, thereby impacting upon personalized medicine, is discussed.

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Introduction to personalized medicine

The testing of individuals for genetic predisposition to disease is already a reality and commercialization of this activity has begun. However, in order to gain the full clinical benefits from this type of information, it will be necessary to correlate it with functional data; *in vivo* diagnostic imaging offers one option. With the publication of the first complete draft of the human genome in 2000 [1], came a flood of speculation and expectation as to the likely impact on the management of human healthcare. Terms such as personalized medicine or individualized medicine became widely adopted by the serious scientific press and national newspapers. The perceived wisdom is thus: very many of the major diseases within the Western world – cancer and heart disease to name but two – have a genetic component. Therefore, the elucidation of the human genetic code will enable scientists, and ultimately physicians, to predict the relative risk for such conditions on a person-by-person basis [2–4]. Furthermore, many drugs available today are only effective in a subset of the population, perhaps as low as 30%, and in others they may have unacceptably high toxicity [5–7]. Again, such phenomena are explicable on the basis of the specific complement of metabolic enzymes that each of us posses by virtue of our genetic inheritance, hence therapeutic regimens may also be individualized to take account of this diversity. The techniques envisaged for use in this area would include both single nucleotide polymorphism (SNP) genotyping and haplotyping, often incorporating some means of high-throughput screening technology, or, more recently, microarray-based techniques. Several excellent reviews have appeared which describe the details of these approaches and these will not be repeated here [8]. However, even assuming that it will become cost effective to profile the genomes of every individual, there remains one major flaw in such arguments. The vast majority of diseases arise from highly complex and currently unpredictable interactions between multiple gene products and a variety of environmental factors. As a result, it may be possible to put a relative risk to any individual based on their genetic profile, however, this risk will define neither whether this person will actually become ill, nor when such an illness will become phenotypically evident. This genetic information alone is of course extremely valuable because it permits individuals to make informed choices about lifestyle or perhaps whether to start prophylactic treatment. Some impressive studies have appeared in the recent scientific literature which serve to illustrate both the power and also the limitations of genetic analysis alone. In one particular example, Shipp and coworkers

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provide compelling evidence that lymphoma patients can be differentiated at the time of diagnosis by virtue of specific patterns of mRNA expression. Furthermore, the particular profile of genes expressed is linked to the likelihood of positive response to the current therapeutic regimen. Conversely, those with the opposite genetic profile at the time of diagnosis were unlikely to benefit from the treatment, with the clear implication that a radically different approach should be adopted for these individuals [9]. However, in neither group would genetics dictate precisely which therapy to use, nor the frequency with which it should be administered. In order to achieve this, the treating physician would need the ability to monitor individual tumor sites within individual patients in order to more precisely rationalize therapy. It is clear then, that even armed with such strong genetic information, more is needed in order to optimize clinical decision making.

Before speculating further as to the potential future interplay between genetic predisposition and positron emission tomography (PET) imaging, it is necessary that one attempts to produce a working definition of personalized medicine. A description has been selected which was used in a recent survey conducted on behalf of Amersham PLC (Buckinghamshire, UK) by Harris Interactive, Inc. (NY, USA) to test consumer and physician attitudes towards healthcare and personalized medicine [101]: personalized medicine is about tailoring the prescription to the individual based on his or her genetic makeup. Everyone has a different genetic makeup and may respond differently to the same medication. Personalized medicine would allow a physician to prescribe the right medicine for each patient based on his/her genetic makeup, thus reducing side effects and increasing effectiveness. The right medicine for the right patient at the right time with the right outcome.

Interestingly in this survey, which included 748 consumers and 200 physicians, the majority of those questioned (84% consumers and 88% physicians) were either somewhat, very or extremely positive about the potential impact of personalized medicine on the future of healthcare. However, the expectation as to when personalized medicine may actually be available ranged considerably, the average among patients being 9 years and physicians 12 years. The reality is of course more difficult to define; some elements are already available, others, perhaps as yet unforeseen, are much further in the future. However, from this definition of personalized medicine, it is in the identification of the right time that PET and molecular imaging has the most to offer. This is for the simple fact that, regardless of genetic risk factors, the actual manifestation of disease and therefore the optimal treatment regimen cannot be accurately predicted on an individual basis using genetics alone. PET imaging is the most sensitive *in vivo* imaging technique that has broad medical application and as such, can play a key role in delivering this vision of personalized medicine.

In vivo molecular & functional imaging

Modern *in vivo* diagnostic imaging techniques are able to provide an exquisite range of detailed and quantitative information from within the living subject, generally in a noninvasive fashion [10–12]. While there is a considerable range of approaches or imaging modalities available to the physician, they can essentially be divided into two types: structural imaging techniques and functional or molecular imaging techniques, or indeed those which can derive a combination of both (FIGURE 1 & TABLE 1). The structural techniques include x-ray and computerized tomography (CT), which is able to show fine levels of structural information with a spatial resolution of around 500 µM. Ultrasound imaging is also a high-resolution structural imaging technique primarily used for soft tissue. Although both

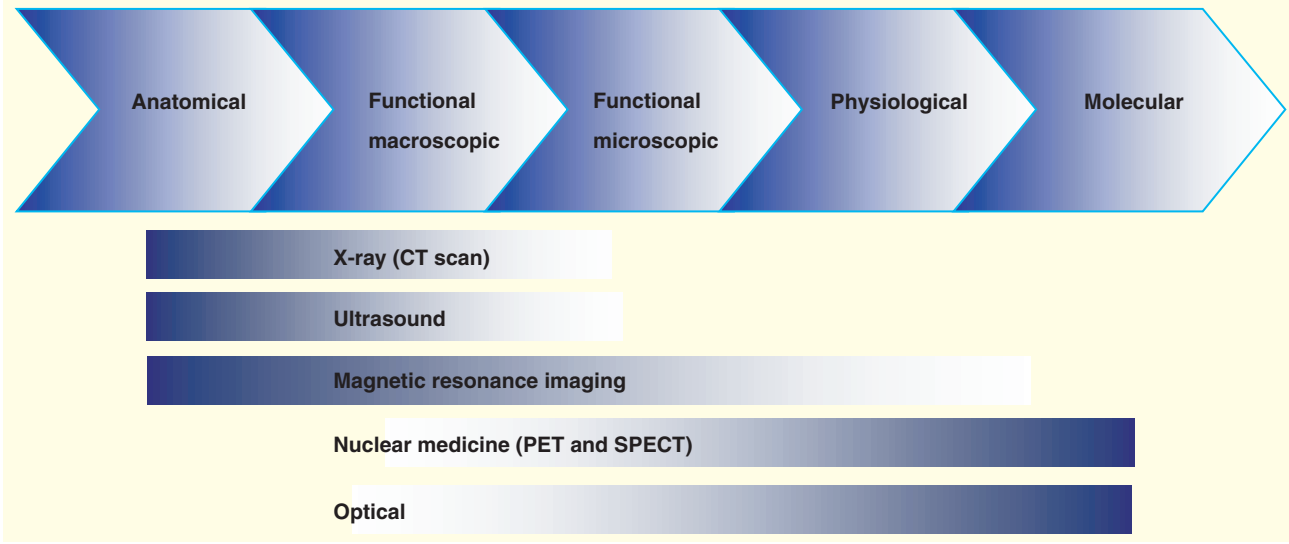

Figure 1. Diagnostic imaging modalities and their key characteristics. A range of noninvasive diagnostic imaging procedures are available. It is currently only really the nuclear medicine techniques (PET and SPECT) which are capable of routine clinical imaging at the molecular level.
CT: Computerized tomography; PET: Positron emission tomography; SPECT: Single photon computerized emission tomography.

Table 1. Diagnostic imaging modalities and their key characteristics.

Imaging technique	Mode	Spatial resolution (range)	Target sensitivity (range)
X-ray/CT	Anatomical	300 µM	Low (>mM)
MRI	Anatomical	800 µM	Low (mM)
Ultrasound	Anatomical	500 µM	Medium (500 nM)
SPECT	Functional and molecular	5–10 mm	High (nM–pM)
PET	Functional and molecular	2–8 mm	High (nM–pM)
Optical	Functional and molecular	0.1–5 mm	High (nM–pM)

The spatial resolution and target sensitivities are derived from a combination of intrinsic properties of the techniques themselves and the particular combination of contrast agent and imaging protocol used. The figures provided are intended to demonstrate the relative clinical capabilities of the different imaging modalities rather than to represent absolute values.
CT: Computerized tomography; MRI: Magnetic resonance imaging; PET: Positron emission tomography; SPECT: Single photon emission computerized tomography.

ultrasound and magnetic resonance imaging (MRI) can be used to derive a degree of functional information, it is really the nuclear medicine techniques of single photon emission computerized tomography (SPECT) and PET which are the dominant functional imaging modalities in clinical practice today [13,14]. While SPECT and PET imaging cannot generate the very high spatial resolution associated with CT or MRI scans, the sensitivity and specificity of these techniques is unrivalled. Furthermore, the nature of PET imaging provides the potential for production of highly quantitative images. Together, these characteristics of PET imaging render it well placed to play an important and growing role in disease management. This is because the first physical manifestation of any disease occurs with specific alternations at the molecular and functional level; early detection of such disease foci is therefore dependent upon imaging techniques of high sensitivity and specificity.

PET diagnostic imaging

PET imaging relies upon the radiolabeling of a specific molecule (or vector) with a PET radioisotope. Many such PET isotopes have been used within the confines of preclinical and clinical research, but the most important ones at the current time are ^{11}C, ^{18}F, ^{13}N and ^{15}O. These isotopes have varying half-lives and other properties which significantly impact upon their suitability as viable candidates for diagnostic imaging applications (TABLE 2). The half-life consideration is of paramount importance as it impacts upon the very practical considerations of manufacture, distribution and use of the final PET-labeled vector. The example of the commonly used PET agent ^{18}F-labeled 2-fluoro-2-deoxyglucose ([^{18}F]FDG) can be used to illustrate this point. ^{18}F is produced on a cyclotron as ^{18}F-fluoride. This is then incorporated into the [^{18}F]FDG precursor mannose triflate, with chemical deprotection achieved, a purification carried out and quality control checks all made prior to administration in the hospital PET imaging center. From the moment that the ^{18}F-fluoride is available, the clock is ticking; the half-life considerations for ^{18}F mean that if a patient dose of approximately 15 mCi is required 7 h after the ^{18}F was made on the cyclotron, an initial dose of over 220 mCi would be needed (TABLE 3). The complex logistics and time limitations accompanying such processes have effectively forced the adoption of highly automated methods of preparation of PET agents. Once the labeled PET agent is prepared, it is injected via the intravenous route and the subject is then imaged using a PET camera, according to the imaging protocol. PET isotopes decay through the emission of β^+ positrons, which travel into the surrounding tissue. In the case of ^{18}F, the β^+ energy is in the range of 0.24 MeV, giving it a tissue path length of approximately 0.35 mm. The β^+ will rapidly undergo an annihilation reaction resulting in the production of a 511-KeV coincident γ-ray pair that can be externally examined by an array of detectors in the PET camera. This information is then processed according to specific software algorithms and final quantitative images are produced.

PET imaging has been in use within the clinical research environment for many years. The first instruments and PET images were produced in the 1970s in the University of Pennsylvania (PA, USA), and while the image quality was not what is expected today, the information produced was astonishing. For the first time, the visualization of active biological processes (in this instance metabolism) could be made noninvasively in healthy human subjects. However, this technology was still in its infancy and not widely available beyond a few specialist research centers. Indeed, this remained the case for around 30 years due to both technological and financial considerations. The situation today is very different and clinical PET imaging with [^{18}F]FDG is a reality in many developed countries. It is estimated that in excess of 300,000 such scans were performed in the USA alone in 2002 across a variety of applications, although dominated (~95%) by the field of oncology; this number is predicted to grow significantly over coming years (FIGURE 2) [15].

[^{18}F]FDG is an analog of glucose which is transported into cells through the glucose transport proteins and accumulates in a manner that appears to relate to the metabolic activity of that particular cell (FIGURE 3). [^{18}F]FDG is transported into cells through the glucose transporter isoforms (GLUT) down a concentration gradient by a process of facilitated transport. Once inside the cell, the [^{18}F]FDG molecule is rapidly phosphorylated

Table 2. Commonly used positron emission tomography isotopes and their physical half-lives.

Radioisotope	Half-life (min)
^{15}O	2.07
^{13}N	10
^{11}C	20.4
^{18}F	110

by hexokinase at the 6-position to produce the 6-phospho form of [^{18}F]FDG. This phosphorylation event serves several important purposes with respect to the accumulation and retention of [^{18}F]FDG, which are essential to the utility of this important radiopharmaceutical. First, the action of hexokinase serves to keep the free intracellular glucose concentration relatively low, thus supporting further accumulation down a concentration gradient. Second, this form of [^{18}F]FDG is not transported by the GLUT proteins and is therefore trapped inside the cells, save for some relatively low-level dephosphorylation. Finally, the 6-phospho-[^{18}F]FDG cannot be further metabolized, as glucose would be, due to the 2´ fluoro substitution, again supporting the continued accumulation of [^{18}F]FDG inside the metabolically active cell. In general, cells or organs with relatively high metabolic activity will accumulate relatively more [^{18}F]FDG than their normal counterparts, thereby generating a hot spot. Tumor cells tend to have a high metabolic index and will therefore, with some notable exceptions, be clearly visible on [^{18}F]FDG PET scans [16–20]. However, despite the undoubted utility of [^{18}F]FDG as a general PET agent for patient management in oncology, it is apparent that this tracer only really exploits some of the features of PET. Therefore, while [^{18}F]FDG-PET has helped to highlight some of the huge potential that PET has in personalized medicine, there is clearly some way to go. If one reflects on the real prowess of PET imaging, it is in the three areas of sensitivity, specificity and quantitation that PET technology excels.

[^{18}F]FDG can be thought of as a labeled glucose; that is, it is transported into and (partially) metabolized to a greater or lesser extent by every living cell in the body. Obviously, this property has been key to the general utility of [^{18}F]FDG across many oncology applications and also in cardiology and neurological disease. However, one of the three important properties of PET has clearly not been exploited, namely that of specificity.

Expert opinion

Unmet medical needs: the driving force behind PET & molecular diagnostics

Any consideration of how PET may be used in the future and how this use may be linked in some way to personalized medicine must begin with an assessment of unmet medical need. Beyond this, the question of how such need can best be addressed and whether PET is the most appropriate technique to address it must be pursued. This point is perhaps best illustrated by considering some topical issues which are under active investigation by both academic and industrial researchers. The first of these concerns the field of oncology and whether (or indeed how) [^{18}F]FDG can be improved upon as a PET tracer. Today, [^{18}F]FDG is used in a range of oncology applications, including early diagnosis, disease staging, determination of response to therapy and long-term follow-up of recurrent disease.

The value of PET imaging for these indications in specific tumor types is recognized in the USA and other countries, with reimbursement for the cost of [^{18}F]FDG and the PET imaging procedure given accordingly (BOX 1).

There are some tumor types which are not easily visualized with [^{18}F]FDG-PET, one clear example being prostate cancer. In this case, the reason for the lack of utility of [^{18}F]FDG stems from the combined effect of low glycolytic activity of prostate tumors and the rapid excretion of [^{18}F]FDG via the kidneys, with consequent accumulation in the bladder [21]. The signal from the bladder is such that it readily obscures any specific accumulation that may be occurring in the prostate gland itself. A second example, also from oncology, is that of detecting primary and secondary tumors in the brain. In this case, the visualization of such tumors is made difficult by the high background accumulation of [^{18}F]FDG associated with normal high levels of metabolic activity in the brain. In both of these examples there is intriguing preliminary data to support the concept that other metabolic PET agents may provide more useful clinical tools. In the case of prostate cancer, imaging with a number of tracers, including both ^{18}F- and ^{11}C-labeled derivatives of choline and acetate, may be useful [21,22]. Similarly, with brain tumors, it appears that the accumulation of various PET-labeled amino acid analogs accumulate to a much greater extent in tumor sites than they do in normal brain tissue, thus providing the enhanced signal-to-noise ratio that is required for successful imaging [23]. A further class of PET tracers which are generating much current interest are the

Table 3. Decay of ^{18}F.

Time post synthesis (h)	Dose in vial (mCi)
0	224.18
1	153.45
2	105.03
3	71.89
4	49.21
5	33.68
6	23.05
7	15.78
8	10.8

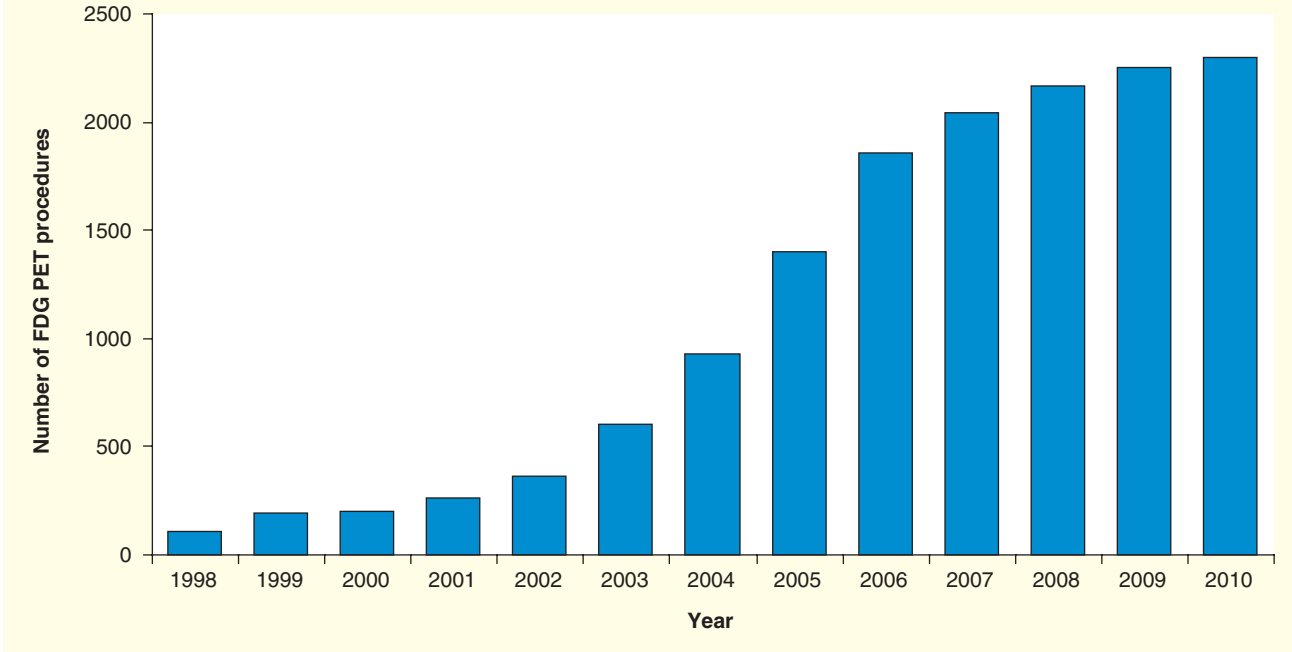

Figure 2. The use of FDG-PET in the USA and its likely growth. The broad utility of FDG has prompted a remarkable increase in its use during recent years. This is expected to continue (the precise magnitude is unclear) in coming years, however, at some point it is likely to be impacted by the availability of new and more specific PET agents. The figures shown here have been compiled from a combination of commercial surveys and company reports and serve only to illustrate the expected growth profile, rather than absolute numbers of procedures.
FDG: 2-Fluoro-2-deoxyglucose; PET: Positron emission tomography.

nucleoside analogs. Such agents appear to accumulate in the DNA of dividing cells in a manner that reflects the mitotic index of such cells [24]. It is envisaged that these agents may have utility in the effective monitoring of therapeutic treatment of cancers which, in the case of [^{18}F]FDG, is somewhat limited by the nonspecific accumulation of [^{18}F]FDG in the associated inflammatory cell populations, which are common in many tumors. Again, preliminary evidence suggests that PET imaging with appropriate nucleoside derivatives may give significantly improved results and indeed much faster responses than can currently be monitored using [^{18}F]FDG. Tumor radiotherapy is one area where new PET tracers within oncology are particularly needed, as described in an excellent review article by Van de Wiele and coworkers [24]. The response of any single tumor to radiotherapy will be dependent upon a range of factors, including the tumor oxygenation status. Identifying biological properties, which may prove relevant to both predicting prognosis and then monitoring response, is a clear medical need. In this regard, the use of [^{18}F]FDG has proven to be of limited use, in part due to the uptake of the agent by infiltrating cells (neutrophils and macrophages) at the tumor site both before but particularly after therapy. This can result in a prolonged period of increased signal at the tumor site following completion of radiotherapy, thus increasing the time before a true assessment of the tumor response to therapy can be made. Once again, PET-labeled derivatives of nucleosides and amino acids are postulated to be of potential use in this application. Other, more specific agents, for example those capable of monitoring tumor hypoxia, those directed at imaging the apoptotic response of tumors to specific therapies and also tumor angiogenesis [24], may also have an important application to the optimization of therapeutic regimens in this patient group [25]. What is without question is that both the development of new anticancer drugs and their optimized use in patients could be improved significantly with access to new, validated PET agents [26]. This is a situation that has also been acknowledged by the National Cancer Institute, which is supporting a range of initiations to further expand research activities in biomedical imaging [27].

The clinical fields of cardiology and neurology (neuropsychiatric diseases) have also adopted PET imaging. In both fields, [^{18}F]FDG has been exploited in the assessment of metabolic changes associated with one particular facet of the disease. In cardiology, it is very important to determine the viability of the myocardium following a heart attack. Perfusion imaging using SPECT tracers is widely used to generate information regarding the localization of the infarct site within the myocardium, but it is less well suited to providing precise information on the status of the cells within the infarct. This is extremely important to perform as the treating physician will need to rapidly determine the need for intervention to restore blood flow to the infarct site in order to salvage resting or stunned myocardial cells. [^{18}F]FDG has been shown to be very effective in achieving this and may play a greater role in this area in the future [28]. In this example, the impact on the individual patient is clear. The rapid identification of viable myocardium and appropriate intervention could result in full restoration of function, thus

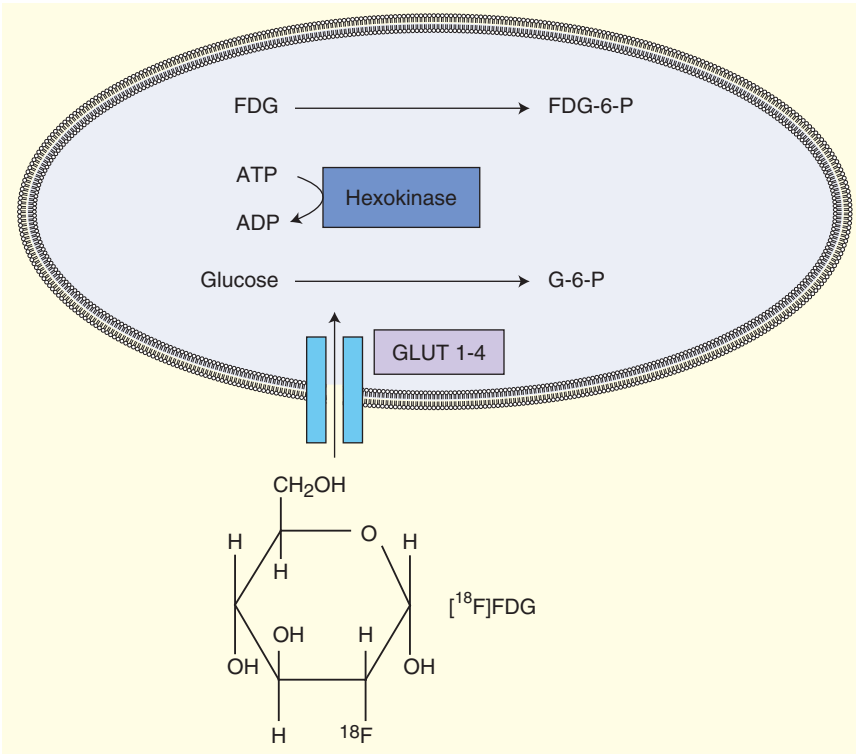

Figure 3. Transport and trapping of [^{18}F]FDG in cells. FDG enters the cell down a concentration gradient via the GLUT transport proteins. FDG is then phosphorylated by the hexokinase enzyme in the same way as glucose, which serves to keep the intracellular concentration low and to trap the phosphorylated product within the cell. The FDG-6-P product is not further metabolized and essentially accumulates within cells, thus providing a signal amplification mechanism to aid imaging. FDG: 2-Fluoro-2-deoxyglucose; FDG-6-P: FDG-6-phosphate; G-6-P: Glucose-6-phosphate; GLUT: Glucose transporter isoform.

reducing the chances of further morbidity, or indeed mortality, in individual patients. Other unmet medical needs in cardiology will require new PET radiopharmaceuticals. The underlying cause of heart attacks in the majority of patients appears to be the presence of the atherosclerotic plaque. While most healthy adults in the developed world will likely have such lesions in their coronary arteries, it is the presence of the so-called unstable or vulnerable plaque which is associated with high risk. If it were possible to visualize these in a noninvasive manner in at-risk populations, it would be possible to intervene, perhaps with a combination of pharmacological treatment and lifestyle changes, to reduce the chances of disease progression (FIGURE 4). To this end, there is a considerable effort within the research community to identify the key pathological features of the unstable plaque to allow rational design of new targeted PET tracers [29]. In this case, the complexities of imaging small hot spots within the rapidly moving coronary arteries may best be served by a combination of PET with a structural imaging technique, such as CT or MRI.

In various neurological conditions it is also possible to visualize alterations in glucose metabolism associated with structural and functional changes in the brain. In the case of Alzheimer's disease (AD), reduction in [^{18}F]FDG metabolism in the frontal and parietal cortices can be visualized [30] and these areas of the brain are known to be directly associated with the hallmark amyloid pathology present in AD. Several significant questions remain with respect to the clinical utility of [^{18}F]FDG in suspected cases of AD. One such question relates to the specificity and sensitivity with which [^{18}F]FDG may be capable of identifying AD patients, particularly at early stages of the disease. This is because the metabolic changes that are detectable with [^{18}F]FDG may only manifest in relatively advanced patients, thus potentially reducing the time window for the application of potential therapeutics which may impact disease progression. This has prompted significant efforts to identify more specific PET tracers which may be able to image the hallmark amyloid pathology directly. Recent results from studies with two such probes provide exciting evidence that this may be possible. The [^{18}F]FDDNP tracer was developed by Barrio and coworkers at the University of California, Los Angeles (CA, USA) and by virtue of its affinity to β-amyloid has shown preliminary efficacy in suspected AD cases [31]. A second group, Klunk and Mathis at the University of Pittsburgh (PA, USA), in collaboration with the Uppsala (Sweden) PET group of Langstrom and coworkers, have produced similar data with a different class of amyloid-binding compounds based on the benzthiazole dyes [32]. While there is still a very considerable way to go in order to prove the clinical utility of such agents, particularly in the eyes of the regulators, the preliminary data are indeed encouraging.

Box 1. Reimbursed positron emission tomography procedures in the USA (Centers for Medicare and Medicaid Services schedule).

Oncology

Solitary pulmonary modules, non-small cell lung carcinoma, colorectal cancer, lymphoma, melanoma, esophagel, head and neck and breast cancers

Oncology proposals for 2003

Brain, cervix, pancreas, testicular and small cell lung carcinoma

Cardiology

Myocardial viability

Neurology

Refractory seizures

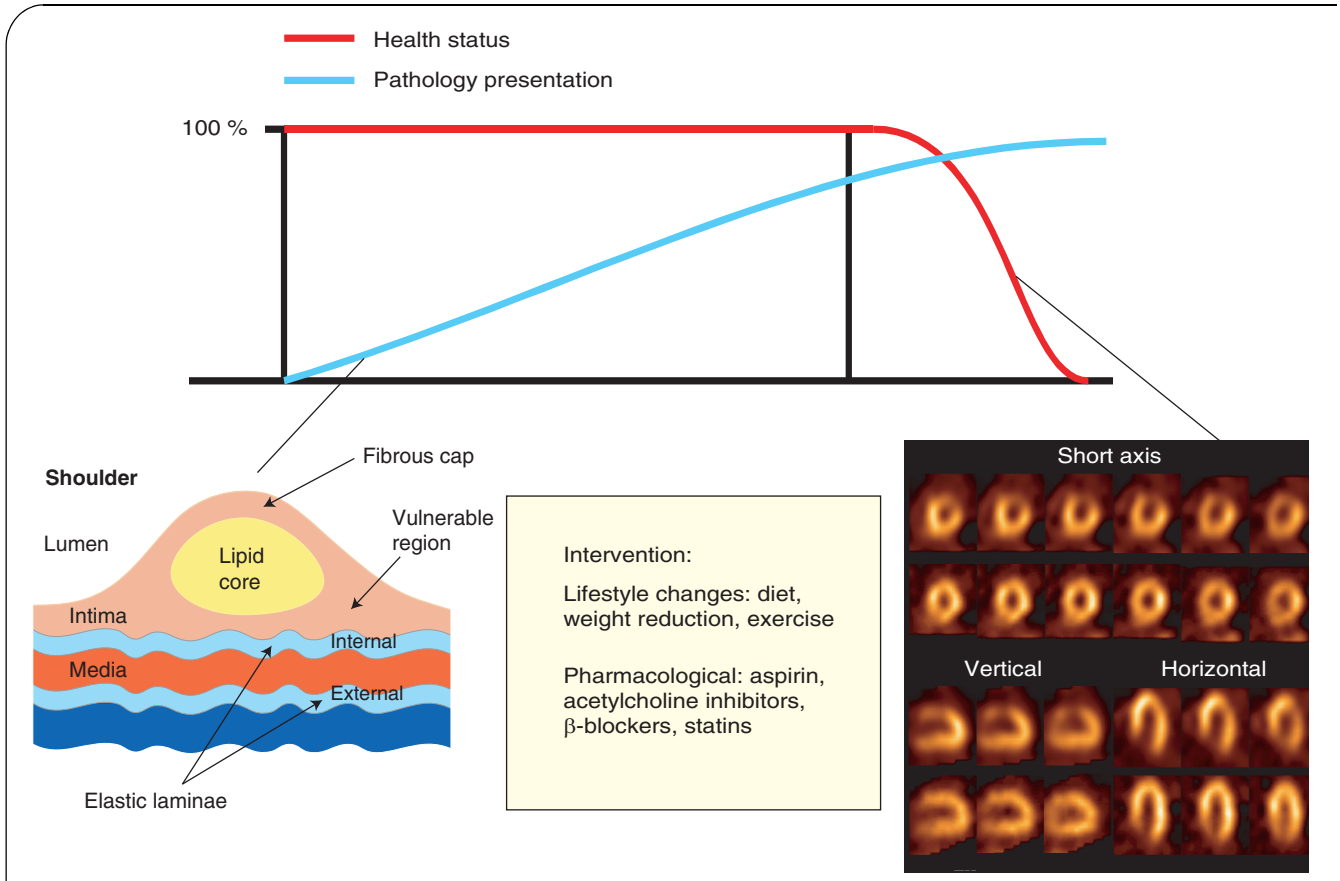

Figure 4. A potential future role for positron emission tomography in the management of cardiovascular disease. Imaging of the effects of heart attacks is achieved today using single photon computerized emission tomography nuclear perfusion imaging. This generates excellent images to show areas of myocardial perfusion deficit (right-hand side). This event is often preceded by a build-up of so-called unstable or vulnerable plaques (left-hand side) in the coronary arteries. Identification of such lesions in high-risk individuals would allow appropriate clinical decisions to be made, potentially lowering the risk of future heart attack.

The integration of amyloid imaging PET techniques with the testing of genetic risk factors, such as the apo E4 genotype, in the management of AD patients is clearly becoming a possibility.

Access to new PET diagnostic agents

The degree to which PET imaging will impact the move towards personalized medicine is therefore intimately linked to the availability of new and approved PET agents. Furthermore, while the needs for new and approved PET radiopharmaceutical products is clear, there is a real question of how such agents may be made available. Clinical access to such specific targeted molecules for development as candidate PET radiopharmaceuticals is a potential limiting factor in the future development of clinical PET imaging. The development of such PET radiopharmaceuticals is dependent upon four key elements:

- Validated, pathology-specific molecular and cellular imaging targets
- Vector molecules with optimized characteristics for *in vivo* imaging
- Reliable and robust radiolabeling chemistry for rapid labeling of imaging vectors
- Regulatory approval and reimbursement of new PET radiopharmaceuticals and procedures

In order to successfully address each of these requirements, it is likely that broad partnership between academic researchers, the pharmaceutical industry and the specialist imaging companies will be needed. Only in this way can adequate access to each of these enabling technologies be assured. For example, much of the understanding and characterization of disease pathology at the molecular level is being generated through collaborations between basic scientists in academic institutes and pharmaceutical companies. From this work, large numbers of potential therapeutic and diagnostic targets are being identified. Many of the therapeutic leads that will arise from this work will be unsuitable for therapeutic application for many reasons, the most common being poor oral availability, high toxicity and inappropriate therapeutic window.

However, such candidates may potentially make good leads for further modification as PET agents. This is because the three parameters listed rarely (if ever) come into play in PET since PET radiopharmaceuticals are given by intravenous injection and at extremely low chemical doses, so low that pharmacological activity and toxicity are very rare. However, a

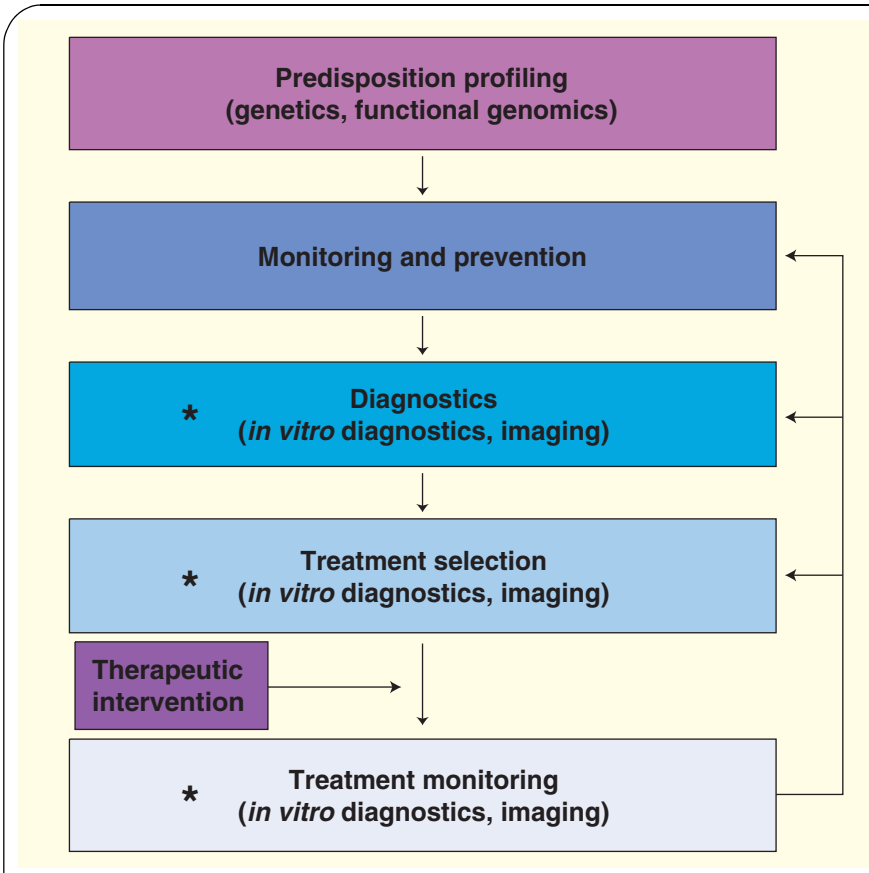

Figure 5. Evolving medical practice and the potential role for positron emission tomography in personalized medicine. There is clear potential for positron emission tomography imaging (indicated by * in the figure) to play a key role in the emerging clinical paradigm of predictive and preventative medicine. The sensitivity and quantitative nature of this imaging technique makes it well suited to monitoring changes in high-risk populations, for example those genetically predisposed to disease.

pharmaceutical lead structure will rarely be suited directly to PET imaging applications and considerable medicinal chemistry input will likely be required to produce PET tracers with acceptable imaging characteristics. Specifically, parameters such as appropriate biodistribution, rapid clearance and route of excretion from the body will all be key determinants of imaging and diagnostic efficacy and lead candidates will often have to be engineered in order to successfully address these considerations.

PET chemistry as an enabler

The full clinical development and approval of a new PET radiopharmaceutical then leads to the question of how to provide access of this product to the clinician. While the growth of PET centers and PET procedures is predicted to rise quite dramatically, it is clear that issues of cost and access could restrict growth of the technique. A key factor here is the investment costs associated with establishing a PET facility. Purchase and operation of the PET camera, or perhaps a combined PET–CT system, in itself is expensive. However, access to PET radiopharmaceuticals requires either building and running a cyclotron and PET manufacturing laboratory, or being able to access PET radiopharmaceuticals from a commercial supplier. Even if such a commercial supply can be accessed, the availability of radiopharmaceuticals beyond [^{18}F]FDG is still questionable because of the difficulty in rapid and high-yielding synthesis of ^{18}F-labeled PET products. One means by which significant expansion of availability and reduction in costs could be achieved is through the provision of kits. In this way, the distribution of PET isotope-labeled, targeted agents could be achieved such that a complex end-user radiochemistry, with its associated high costs, could be avoided. The most likely format for such kit-based products is the provision of a final intermediate which could then be radiolabeled (most probably with ^{18}F) by the end-user, or in a regional manufacturing facility in a manner analogous to technetium kits. To this end, Amersham Health has entered into a research and development collaboration with General Electric Medical Systems (IL, USA) to develop and provide such technology, thereby expanding the future access to a new and increased range of approved PET radiopharmaceuticals.

Health economic considerations

While the technical barriers to providing PET molecular imaging may be addressed, the full potential impact of PET in future medical practice and personalized medicine will only be evident if healthcare providers are willing to pay for it. The willingness to do this will be based upon increasingly stringent considerations of value and how PET may contribute to a more effective use of resources [33]. The hypothesis to be tested will be along the lines of: early and accurate diagnosis and improvement in the management of disease has benefit for both patients and healthcare providers, care givers and financiers. The current genetic screening services offered by some organizations may provide a glimpse into a future that will be upon us very soon. The ability to identify individuals from birth and assess their relative lifetime risk of developing a range of diseases will come; in some cases these associations have already been identified. Access to the information supplied by specific genetic associations with disease will radically transform clinical management in many ways. One such way is the capacity to promote lifestyle changes (manipulate the influence of environment factors) in targeted groups, thus empowering individuals to influence disease penetration rates. A second way in which the management of these high-risk patients will change is in the requirement for targeted screening. There are current debates about the value of screening in large diverse populations [34]; such arguments become very

much simpler in the context of clearly-defined risk factors. Regular screening, including the use of *in vivo* diagnostic imaging techniques, will undoubtedly benefit the management of these patients. Genetic predisposition will only ever provide information about relative risk; expression of the full disease phenotype is influenced by other factors. Therefore, the ability to monitor physical symptoms of disease in these patients, the very core strength of imaging, will be required to make a full assessment of disease progression and therefore to direct treatment.

The question remains, however, as to whether the benefits that PET imaging can offer in this situation really represent value for money. Detailed analysis of the costs and benefits associated with, for example, directing specific treatments, which may be both expensive and highly toxic, to the correct subset of the population who will benefit is required. Furthermore, the early and accurate diagnosis of disease will allow early intervention with the associated improvements in prognosis. Early detection of cancer remains, despite advances in surgical and medicinal treatments, the most significant prognostic factor in determining patient outcome. Once again, however, substantial efforts are required in order to present these arguments in a coherent and persuasive way to those bodies who control the allocation of healthcare budgets. Other, even more complex scenarios also exist, where the ability to diagnose and characterize early disease through PET imaging may be possible but where no efficacious therapy exists for treating the condition. In this case, there is of course the ethical dimension as well as the economic question. There may indeed be enormous benefit to both the patient and the clinician in being able to confirm, or indeed rule out, the presence of disease, perhaps therefore reducing the need for other expensive and distressing diagnostic examinations, thereby avoiding the use of unnecessary medications. There can also be significant value to the patient in being able to recognize the implications of a diagnosis at an early stage and make plans in light of this information. These questions, while raising significant ethical and philosophical points, as well as practicalities of resource allocation, may be difficult but have to be faced. The combined power of genetic predisposition testing and molecular imaging will continue to force such issues to the top of the healthcare agenda.

Five-year view: the expanding role of PET in clinical management

PET imaging has the potential at a technical level to contribute significantly towards disease management and in doing so, bring the vision of personalized medicine significantly closer to reality. The question is how much closer to realizing this vision will we really have moved within the next 5 years? There is no doubt that wider access to [^{18}F]FDG-PET imaging will become a reality for many people in the developed world within this timeframe. The continued spread of this technology across the USA and Western Europe is widely anticipated by the hardware manufacturers and healthcare providers alike. Also, in Asia, notably in Japan, the further expansion of [^{18}F]FDG-PET is also envisaged with recently announced plans to expand the commercial manufacture and supply of [^{18}F]FDG-PET in this country. For those with access to [^{18}F]FDG-PET, it can be argued that the potential benefits of personalized medicine will become closer to reality. The acceptance and adoption of specific *ex vivo* tests to identify genetic predisposition is likely to become more widespread in specific populations. This will be a further manifestation of the so-called predict-and-prevent approach to medical practice which is becoming more widely accepted in the developed world. As has been seen, PET has major attributes which means that it will be well placed to play a key role in this new paradigm (FIGURE 5). The practice of screening at-risk populations using relatively low-cost *in vitro* (*ex vivo*) tests will allow the further streaming of individuals on the basis of risk. This risk profiling will be used to determine, in the first instance, the requirement for diagnostic imaging, thus allowing therapeutic intervention to be directed to the very first stages of disease. Subsequent use of molecular imaging techniques, either to aid in the selection or optimize the dose of a particular treatment or in monitoring disease recurrence, will again support the personalization of patient management. However, the widespread adoption of [^{18}F]FDG-PET has been closely linked to approval of the PET radiopharmaceutical itself and subsequent reimbursement of the procedure. The challenges of securing approval and reimbursement for novel PET radiopharmaceuticals will undoubtedly reduce the likelihood of widespread access to new PET procedures.

Diagnostic imaging companies with proven expertise in developing commercial radiopharmaceutical products, principally within the SPECT area, have already demonstrated significant commitment to this field. If the opportunities afforded by PET are to be fully realized, it will be through access to new approved PET radiopharmaceuticals. However, if it is accepted that access to approved radiopharmaceutical products is an essential component of the future role for PET in personalized medicine, the issue of return on investment is inevitably raised. PET imaging can essentially be as specific as required. Within the pure research environment this is seen as only beneficial. However, for an industrial company there inevitably has to be a sound commercial as well as a medical case to support radiopharmaceutical development. The costs and income associated with highly specific agents may never be cost effective. It can therefore be predicted that that the major focus will be in the development of new general markers with wide potential utility but with significantly improved specificity for certain applications. Examples may include new markers with application across different tumor types, perhaps including amino acid analogs, markers of DNA synthesis and angiogenesis imaging tools. Beyond this, more specific agents with application in diseases with large incidence and prevalent populations are likely to provide an important focus. Medical conditions, such as AD and cardiovascular disease (atherosclerotic plaques), would both fall into this category.

Once these are available, medical practice and healthcare providers will have to decide how such imaging opportunities are ultimately combined into patient management paradigms.

There is little doubt that within a 5–10-year horizon, advances in our understanding of the genetic basis of disease, combined with access to new PET radiopharmaceutical products, will provide a significant opportunity to improve the management of a range of major human diseases. These improvements in disease management will positively impact both the patient and the treating physician, but ultimately the cost effectiveness of medical treatment. This is for the simple reason that the most important prognostic factor for many of the major diseases in the developed world remains early detection. The combination of genetic profiling and PET molecular imaging really does represent a major opportunity to optimize treatment on an individual level, while at the same time enabling more cost-effective management of healthcare budgets.

Key issues

- Modern healthcare practices are moving towards a so-called predict-and-prevent paradigm.
- The identification of at-risk populations and the early diagnosis of disease within these groups will facilitate optimal delivery of healthcare provision in a cost-effective manner.
- Positron emission tomography (PET) molecular imaging is a proven clinical imaging technique with unrivalled sensitivity.
- The combination of genetic testing and PET molecular imaging is well placed to provide two key components of the successful implementation of personalized medicine.

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