Personalised Medicine and Medical imaging: Opportunities and Challenges for Contemporary Healthcare

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Personalised medicine

Personalised Medicine (PM) refers to the use of a person's genetic information in tailoring strategies for the detection, treatment and/or prevention of a disease(1). Developments in genomics have led to the consensus among scientists and clinicians that PM holds the potential to revolutionise medical practice, especially in oncology(2). PM is aimed at delineating sub-types of patients based on their disease mechanisms and their particular response to therapies. It is based on the emerging knowledge that some underlying molecular variations are responsible for certain diseases and they in turn can be managed by certain therapies (3). This is a departure from the 'one size fits all' approach where patients with similar ailments are given the same type and dose of medication without knowing who might benefit most or conversely who might suffer toxicity and adverse drug reactions(4,5). The complexity inherent from the forgoing has perhaps impeded the early realisation of the dream of personalised healthcare. For example, while some diseases (rare inherited) are caused by mutations in a single gene, most other diseases are caused by a combination of hereditary and environmental factors and therefore pose another layer of complexity(6).

PM is aimed at ensuring that the right patients get the right dose of the right treatment at the right time (7). Personalised medicine, stratified medicine and precision medicine are used interchangeably within literature to denote the same concept, even though their specific meanings are nuanced. In fact, the term stratified medicine replaces personalised medicine in some literature to avoid the potential confusion that, treatment or prevention strategies are tailored specifically to a person rather than sub-groups of patients(8). Medical imaging by its nature has always attempted to be personalised and looks poised to be essential in the future of personalised medicine. Imaging biomarkers can be used for stratification of patients in terms of staging disease or intervention. Medical imaging is also going to be vital in personalised therapy planning, delivery and monitoring of treatment effect and disease progression.

Arguably, PM could be viewed as an iterative process of tailoring treatments to patient characteristics and not as an innovation that has just occurred. Salari, Watkins and Ashley(9) argue that a patients' environment, behaviour and genes have been (for years) incorporated into patient treatment decisions, risk stratification and drug response projections. However, 'this one size fits all' paradigm of therapy has been costly in terms of toxicity and inefficiency and has led to an 85% failure rate of cancer therapies in clinical trials(10). Notable successes in genetic profiling of tumours such as positivity to human epidermal growth factor receptor-2 (HER2) resulting in an increased success rate of treatment for such patients (11). This and other developments has driven optimism within the sector that PM has the potential to reduce the exposure of patients to ineffective therapies, reduction in toxicity, produce longer patient survival and make such targeted treatments more cost effective (10)

Drivers (Technological)

The mapping of the human genome DNA sequence(12,13) and the mapping of variation in DNA and their distribution in populations (13) marked the biggest driver in the awareness of disease pathways in molecules (14). Informed by the above achievements PM is taking various forms including the identification of cancer risk, targeted therapy resulting from the identification of biomarkers, prediction of drug response (pharmacogenetics/genomics) and the prediction of the chances of disease recurrence through the analysis of cancerous tissue(15). This has been followed by further genomic sequencing projects championed by various western governments such as the 100,000 genome project in the United Kingdom and the effort to sequence the genome of 1 million people in the USA. For PM to be successful, identification of the link between patient responses and biomarkers is essential. However, environments and external factors should also be considered. Most diseases (e.g. coronary artery disease (CAD)) are polygenic in nature. For example, with regards to CAD a recent literature review found that 25-50% of the mutations/variants identified occur in between 50-75% of the population but only confer a risk of only 18%(60). Such weak effects could be explained by the interplay of genetic and environmental factors.

Atkinson and colleagues(15) define biomarkers as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses". These biomarkers are therefore important in the identification of the classification of sub-populations of patients who might be predisposed to a disease or respond to a therapy. As a consequence of the Human Genome Project and the International Haplotype Map project more than 1300 loci for about 221 diseases and traits are available through the validated Genome-Wide Association study (GWAS) (17). Through these biomarker associations it has been possible to predict the risk of people developing a disease such as cancer. Biomarkers are broadly classified as prognostic markers, predictive markers or both. Prognostic markers provide information about a patient characteristic that has the potential to affect the course or outcome of the disease. Predictive markers on the other hand refer to patient characteristics which can predict a patient's likelihood of benefiting from a treatment or intervention (18).

Based on an individual's genetic sequence it is becoming possible to predict adverse reactions to medication. Through the assessment of individual differences in key enzymes associated with the metabolism of drugs, pharmacogenomics is enabling the ability to avoid toxicity of drugs (such as Tamoxifen) by either avoiding them or reducing doses (19). For example, Azathioprine (AZA) as a pro-drug, is an immunosuppressive medication. It is mainly used in inflammatory bowel disease for the maintenance of remission and also the closure of fistulae(20). The metabolic pathway of this drug

results in the production of the active metabolite 6-thioguanine nucleotides (6-TGN). Excessively high levels of 6-TGN results in myelotoxicity and this is in part dependent on the relative amount of the inactive enzyme thiopurine methyltransferase (TPMT). The level of TPMT has been found to exhibit genetic variation (TPMT*2, TPMT*3A, and TPMT*3C genes) and as a result genetic testing is advised before the administration of the drug (21).

Patients benefit from an intervention that is best suited to them and the possibility of toxicity to the patient is reduced. It is believed that 6.5% of all admissions are related to adverse drug reactions where patients stay for an average period of 8 days stay, occupying 8000 beds and costing $1.3 1billion per year to the NHS in the United Kingdom(22,23) The benefits to patients and the national purse are obvious. It is important, however, to recognise that the success of PM within the context of genetic testing depends on many factors. For example, the public's acceptance of genomic technologies may depend on data security, insurance, discrimination and commercialisation of genomic information, thus requiring a critical lens. Also, whilst the cost of genetic sequencing keeps reducing, the costs are quite high (just over $1000)(24) and may serve as a barrier to PM regardless of the paying/health economic model.

Drivers (Commercial)

The traditional Fully Integrated Pharmaceutical Company (FIPCO) model (which relies on a few blockbuster drugs to generate enough revenue to compensate for the high R&D expenditure) is being challenged by a trend of declining R&D productivity within the industry since 2003(25). In addition, patent expiry of major drugs of a good proportion of the leading pharmaceutical companies is expected to reduce sales by more than 50% due to the influence of generic drugs (26). Furthermore, due to increased health care costs and unfavourable public perception of pharmaceutical companies, there has been a push by governments and payers to contain costs and the application of more stringent requirements about drug efficacy. For instance the National Institute for Health and Care Excellence (NICE) does not recommend the use of Benlysta for the treatment of Systemic lupus erythematosus (SLE) because it is not considered as cost effective even though it realised $52.3 million from sales in 2011 (27) .Whereas the cost of drugs is mostly left to market forces in the USA, countries like Japan require a mandatory reduction in drug prices every two years.

Diversification into PM therefore offers a potential strategic alternative to the blockbuster model. There is enough evidence of this paradigm shift with most of the large pharmaceutical companies either acquiring or merging with smaller Biological companies(28). In addition to the increased possibility of replenishing dwindling pipelines, PM also offers some protection against challenges from generics. This means that the pharmaceutical industry has faced a reduction in drug

development within the past decade. Further, a number of drugs are losing patent (commonly known as the 'patent cliff') and thus becoming 'cheap generic drugs'. PM, therefore, offers the industry an opportunity to increase portfolios and productivity. PM involves targeted therapies that have specific modes of action which would be very difficult for generic companies to copy (29). Genetic sequencing as part of PM, by definition, requires that only validated biomarkers go into advanced stages of clinical trials. This has the potential to reduce the length and cost of trials thus offering a new form of stage-gating (30) and efficiency in research and development. While the blockbuster model represented drugs for a high-volume market, the PM model points to a smaller target group. Even though revenues might seem to reduce, the competitive advantage derived from differentiated goods actually results in increased profits driven by margins rather than volume (29) . It therefore indicates that it is possible in theory to obtain similar amount of revenue. With the increased emphasis on drug efficacy by payers, PM through companion diagnostics offers a better chance of reimbursement.

Drivers (Ethics)

In spite of the obvious advantages that could accrue, PM still poses some ethical concerns which expose much complexity (hence constitutes a major driver). These include consent for genomic testing, privacy, confidentiality of genomic test results and equity of access to genetic testing and targeted therapies in oncology. For example, the new General Data Protection Regulations (GDPR) could, affect collection of genomic data amongst the population, yet, this could mean better assurance to the public of the intended use of their genomic data. In short, then, clinicians would have to spend more time in the consenting process thus better informing patients in how their data is going to be used. The cost of such therapies to health care systems is another ethical consideration. These have the ability to affect the extent to which PM is wholly accepted and incorporated into mainstream medical practice. Many patients find it difficult to understand the purposes and complexities associated with pharmacogenomics testing (31) . This is partly due to the vast amount of information that needs to be given to patients before consent and also the potential psychosocial impact germline and somatic testing could have on patients and their families if adverse findings are encountered(32). Recent research by Garfield et al., (33) into consumer familiarity with PM found that 75% (of 602) had not heard about PM and poses a challenge for consenting patients and timely intervention. As a consequence the European Society for Medical Oncology (ESMO) advocates for broad patient consent to allow for further testing to take place without having to re-consent patients(34) . There is also the issue of genetic privacy where concerns have been raised about patient autonomy and the ability to retain control over how genetic information is collected, used and disclosed. This is

particularly important in the context of electronic patient records and is in spite of the genetic information non-discrimination law and moratoria (35). Genetic information non-discrimination laws prevent the use of genetic information in health insurance and employment (US and Canada) while a moratorium in place in the UK doing a similar job. There is concern among some clinicians that some diseases may be so rare that some pharmaceutical companies may not want to invest scarce research and development resources in them. This has led to concerns that the future of PM might be stratified based on socio-economic background and how common a cancer is (32).Even though the shared vision of PM is that all patients with a disease that has a suspected genetic link would have their genes sequenced to allow for targeted therapies, the reality could be that access to genomic testing depends on patients' socioeconomic status, insurance policy and location. Some legitimate questions arise; who owns my genetic information once it is sequenced, the sequence provider or me? Can I be identified? How secure is my genetic information? Who polices the police? How can I be sure that my genetic information would not be used by a corrupt person to frame me for a crime? Very recent research by Anna Middleton and colleagues at the Wellcome Genome Campus suggest that the most concern people have about genetic testing is that their information will be used to frame them for a crime(36). In addition to this, it has been found that genetic databases are skewed towards European Caucasian populations and this makes it difficult in interpreting variant data emanating from minority populations. It is conceivable that if this imbalance is not addressed minority populations would not reap the benefits of PM arising from genomic data (37)

Medical Imaging

It is obvious that medical imaging plays an important role in personalised medicine. This includes all aspects such as diagnosis, prediction and treatment. When patients present initially with signs and symptoms, their route to diagnosis would, in the majority of cases involve medical imaging howbeit in combination with other modalities such as laboratory analysis of body fluids. Therefore, medical imaging is tailored to a person's clinical and personal characteristics to ensure that the correct imaging procedure and modality is used for the right patient while reducing the detrimental effects to the minimum. Examples where imaging procedures are carried out based on patient characteristics include: the use of patient weight to determine the quantity of contrast medium used; weight-based isotope injections (NM);exposure parameters based on patient build (CR/DR/CT); and the use of MRI and ultrasound when imaging children and pregnant women (38).

The detection of diseases before they clinically present can potentially save lives. Medical imaging, through screening aids in the detection of diseases at the sub-clinical level in order to allow tailored preventative measures to be taken. This allows stratification of patients into sub-groups of

risk (low, intermediate and high). This is exemplified in breast, lung and colorectal cancer screening programs(39–41). Also, the use of MRI as a supplemental imaging modality for women at high risk of breast cancer has been found to be very effective in detection even though latest studies suggests its uptake is not as high as expected (42,43). Screening, as it is today (e.g. breast and AAA screening) is based, at least partly, on the thinking that it is more cost-effective to pick up and treat diseases sooner than later in the targeted population. It might be argued, and rightly, that dependence of screening on cost-effectiveness may not necessarily be personalised. There seems to be a tension between the requirements of evidence based healthcare and the need to keep PM strictly personalised.

The location and extent (a proxy for severity) of disease is vital for the choice of treatment. This allows personalised treatment regimens to optimise treatment and reduce adverse effects. A typical example is the staging of tumours. The combination of cross sectional modalities such as MRI and CT with quantitative metabolic information from PET and SPECT imaging has led to better visualisation of cancers. Whole body scanning also aids better detection of metastasis (44,45). As already pointed out, biomarkers play an important role in the selection of the appropriate treatment. In medical imaging prognostic biomarkers are essential in differentiating between aggressive and non-aggressive disease, while predictive biomarkers are able to determine tumour response to therapy. For example PET/CT is able to predict accurately tumour recurrence in breast cancer(46).

One exciting aspect of medical imaging in PM is Radiogenomics. "This is the term used when imaging features are correlated to gene expression"(47). Here a large dataset of information relating to a disease are taken from an image and correlated with gene expression patterns of the disease. The presumption is that whatever is happening at the genetic and molecular level results in the image appearances (48,49). This has been used successfully in areas such as MRI features and gene expression in breast cancer and CT features and gene mutations in renal cell carcinoma (50,51). From this information, determination of disease progression and response can be individualised for patients (52).

The accurate response to treatment is important in PM as it determines whether treatment is continued, adjusted or stopped. In circumstances where treatments are ineffective, discontinuation of treatment would result in patients being offered alternative therapies or spared the side effects of the ineffective one. Medical imaging plays an important role in the assessment of radiotherapy, chemotherapy and image guided intervention response. A typical example is PET imaging of the liver and pelvis to determine tumour response to chemo and radiotherapy (53). More recently Ruth Casey and colleagues have demonstrated the clinical application of in vivo metabolomic analysis using proton-1 magnetic resonance spectroscopy (^{1}H-MRS) in patients with succinate dehydrogenase (SDH) deficient tumours (54). Mutations in the (SDH) subunit genes are associated with a wide spectrum of tumours, including, GI stromal tumours, renal cell carcinomas, and pituitary adenomas.

Their ability of ^{1}H-MRS to capture this is promising for the noninvasive diagnosis, stratification and monitoring of tumour response to targeted treatments(54).

Medical imaging also aids to a personalised approach towards treatment planning. Arguably, a treatment of disease would depend on the individual characteristics of the disease as seen in imaging prior to and during treatment. An example is the use of functional MRI for planning surgery for brain tumours(55,56). MRI is used increasingly in conjunction with intensity modulated radiotherapy (IMRT) with the objective of improving dose delivery to tumours while reducing dose to healthy tissues. Furthermore, the use of image guided radiotherapy for body parts that are prone to movement helps to minimise or avoid radiation to healthy tissue. This guidance is of course tailored and personalised to the patient. Hypoxia arises when living tissues to do not get adequate oxygen supply to cellular metabolic demand. In tumour cells hypoxia can be indicative of tumour aggressiveness and poor outcome. Its detection is therefore important. Hypoxia imaging using [^{18}F]MISO-PET in head and neck cancer helps to detect regions that are resistant to treatment and helps to enhance the treatment of patients when combined with IMRT (57).

Challenges

One of the challenges facing PM is the complexity and heterogeneity of genes and their mutations associated with disease. Somatic mutations have been found not to reoccur in various gene sequencing projects that have taken place. Further sources of complexity occur when the tumours' microenvironment is taken into consideration. GWAS studies also have to account for patients' immune systems which might be a function of their lifestyle (58). This, therefore, requires the need for very effective and rapid modalities for sequencing and the availability of a large amount of information about various tumours or disease mutations against which comparisons could be made. To this end, various initiatives have been launched. The 100,000 genome project launched by the NHS in 2012 for example is aimed at forming the basis of genomic medical services in the UK. Also the stratified medicine innovation platform (SMIP) was launched in 2011 to profile a large number of patient's tumours for biomarkers (10). The availability of multiplex assays and high throughput screening platforms can also help increase the speed of sequencing in the future (59).

A second challenge is the availability of the infrastructure for conducting and interpreting genetic information. The human genome contains over 6 billion data points. The information being generated is vast and research has shown that clinicians struggle to make sense of this vast amount of data (60,61). There is, therefore, the need for education of clinicians and the provision of decision support tools and electronic patient data. To solve this issue various governmental and non-

government institutions are investing into the necessary infrastructure to make PM possible. The UK government for instance is investing $18.1 million in stratified medicine in 2015 and in the same year $215 million was earmarked by the US government for precision medicine projects including the screening of 1million volunteers (62). The NHS has also engaged the services "Deepmind" an artificial intelligence system from Google to analyse patient data. Advances in computer processing (such as quantum processor by IBM) can help analyse vast amounts of data generated (63). Financial resources are needed to deliver the dream of PM. For example, once the efficacy and dosage of a therapy is proven to have genetic link there needs to be the resources and will to make it available to those who need it. For example, NICE (in the UK) recommends the use of Azathioprine for the treatment of IBD. However, it falls short of mandating genetic screening for genetic variants associated for its differential metabolism (it only recommends that clinicians "Consider measuring TPMT activity before starting azathioprine"). This is even though Azathioprine has drug labels containing pharmacogenetic information from the FDA (testing recommended), Pharmaceuticals and Medical Devices Agency, Japan (actionable PGx) and Health Canada (Santé Canada) (actionable PGx)(64) . Such a mandate would make health care authorities legally bound even though the availability of resources is patchy, at best. The funding and infrastructure for genomic screening is at its infancy and it is likely that until these resources are more widely available the health systems would be reluctant to mandate such genomic screening.

There are issues with regulation in terms of drug approval processes and the proliferation of private companies providing genetic testing facilities. For companion diagnostics to be approved both the drug and the test has to meet regulatory standards. Diagnostic test review processes take place in different sections of the Food and Drug administration (FDA). These divisions apply different standards and therefore challenges may exist in bringing such therapy to market(65). Faster development and approval of companion diagnostics as proposed by Schilsky (65) is needed. Due to the media attention that high profile cases mentioned above there seems to be a proliferation of companies offering genetic testing for patients. Unfortunately there are no standardised medical guidelines and quality assurance frameworks available and therefore there is the need for oversight to ensure safety and security of patient's genetic information(66). Whereas self-regulation might be argued by some of these private providers (to reduce costs), arguably the sensitivity of genetic information and the emotive nature of sectors like oncology would suggest direct centralised regulation might be necessary to prevent regulation capture.

A further challenge is the process by which decisions to approve genetic testing and subsequent funding is made. Research has shown much variation in the public and private sector. Private health insurance companies have restrictions on companion diagnostics (placing more emphasis on treatments). Similarly, in the UK NICE places more value on treatments in their computation of cost effectiveness (67). The cost of this class of novel drugs is high and it is hoped

that with increase in knowledge and discovery more drug targets and candidates costs would reduce(68).

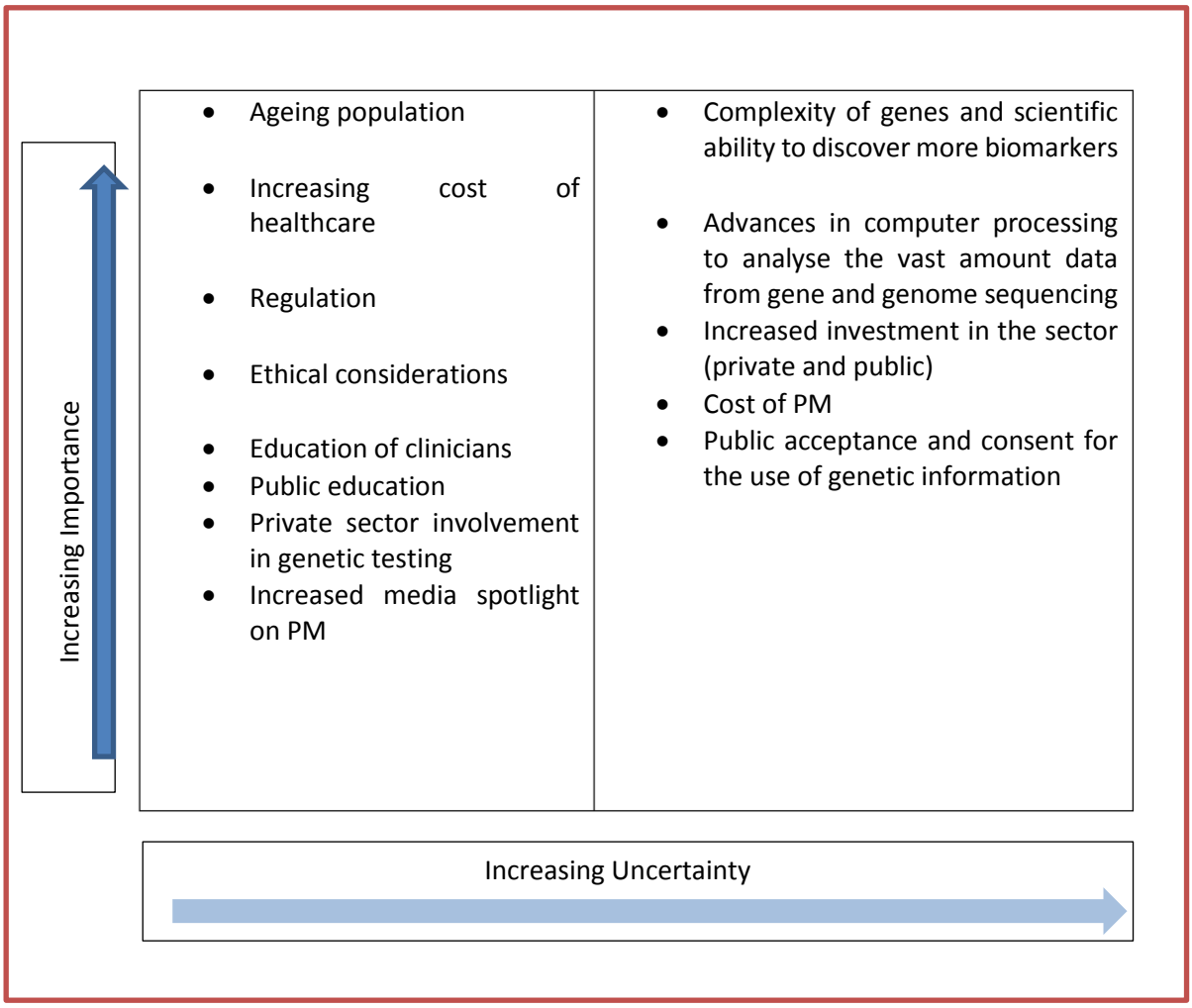

Figure 1 Shows the drivers of the future success of PM ranked according to importance (vertical axis) and uncertainty (Horizontal axis)

Looking ahead

Due to the complexity of the drivers and challenges discussed above, it is difficult to predict what PM would look like in decades to come. Such complexity breeds uncertainty and strategic decisions need to made by governments, health systems and policy makers. Scenario planning is one such tool used for this purpose.

Michael Porter's definition of a scenario is an 'internally consistent plausible view of how the future might turn out (Porter, 1985). Unlike forecasting, scenarios do not necessarily have to be probable. They only need to be plausible. A set of scenarios may present mutually exclusive futures which may be desirable or undesirable. Forecasting aims to identify a plausible and likely future. Scenarios are usually created projecting forwards from present trends. These can then be used to

develop robust strategies for the perceived future. They can be used to position an organisation so that it can respond to any future which arises within a set of scenarios. Bradfield et al. (69) and other authors have written at length about the merits of scenario planning and exemplifies Shell Corporation as an example of an organisation which gained from this exercise during the oil price shock of 1970s. Figure 1 above represents the list and ranking (according to importance and uncertainty) of drivers that may affect PM. However, while high profile leaders and policy makers such as the Chief Medical Officer of the NHS (Dame Sally Davies) is calling for the NHS to deliver the genomic dream in 4 years, the reality on the ground and from the foregoing suggests that this might be unattainable.

Conclusion

It is obvious from the foregoing that PM holds great potential in the future strategy of combating all manner of ailments. This will be driven by the advances in genomic research and the success of analysing vast amounts of data. Further, these advances are capital intensive and financial investment both public and private would be essential. The need to make private investment profitable has to be balanced with the general public good in order to ensure that high ethical principles are maintained and such that targeted treatments for the diseases do not become the preserve of the rich. Medical imaging plays a vital role in PM with regards to diagnosis, prediction and treatment. PM has already entered the clinical practice in many places; it is important that the medical imaging community become conversant with this concept and is prepare to take their place as a relevant partner in PM.

Strategic Recommendations

To ensure the success of PM, the following strategic recommendations are suggested:

- Increased investment genetic studies and computer processing for the discovery of new biomarkers
- Streamlined regulations to address concerns about genetic privacy and confidentiality
- Regulatory incentives to ensure profitability of pharmaceutical industries and equity of access to PM
- Standardisation of genetic testing and documentation

- Regulation to ensure private genetic testing firms do not take advantage of the populace
- Better awareness about PM within the medical imaging community

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