



Progress towards personalized medicine

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Personalized medicine is the tailoring of therapies to defined subsets of patients based on their likelihood to respond to therapy or their risk of adverse events. The advent of improved genomic tools has greatly hastened our understanding of the molecular pathology of diseases, enabling us to redefine disease at the molecular level. The development of molecularly targeted therapies, coupled with improved diagnostic criteria, holds the promise of delivering a new paradigm in drug development. But how far have we come, and how close is personalized medicine to delivering on its promise?

In September 2008, the President's Council of Advisors on Science and Technology (PCAST) published their well-considered report 'Priorities for Personalized Medicine' [1]. Summarizing the outcome of their broad-ranging 18 month review in which they received input from industry, physicians, patients, government agencies and academic scientists, the PCAST report paints a clear picture of the potential for personalized medicine to reshape healthcare provision and economics in the years ahead. Working from the premise of continued rapid expansion in the field of genomics-based molecular diagnostics, the report considers the long-term implications of this growth in molecular medicine on future healthcare requirements. One of its seven recommendations is the development of a strategic, long-term plan to shape public and private research efforts into personalized medicine. Other recommendations cover areas as broad as public research funding, improved regulatory oversight of both diagnostic and therapy-linked testing, removal of reimbursement hurdles to genomic test adoption and the establishment of an office of Personalized Medicine Adoption within the Office of the Secretary of the Department of Health and Human Services.

In itself, this remarkable document provides interesting insight into the impact that the concept of personalized medicine is having on the way we are thinking about future healthcare provision. Taken together with the recent congressional bills on personalized medicine (the Genomics and Personalized Medicine Act

2006 [2] and 2008 [3]), the Health and Human Services Secretary's Advisory Committee on Genetics, Health, and Society report 'Personalized Health Care: Pioneers, Partnerships, Progress' [4], the extensive FDA literature and guidance going back to the Critical Path Initiative in 2004 [5], and the establishments of advocacy groups such as the Personalized Medicine Coalition (The Case for Personalized Medicine Report 2009 [6]), it becomes clear that personalized medicine is likely to play an increasing part in healthcare provision in the years ahead. Indeed, Barack Obama, sponsor of the first congressional bill, is himself a long-standing supporter of personalized medicine. The concept of personalized medicine, therefore, is guaranteed to be tested in the years ahead, but will it deliver the wide-ranging benefits that its supporters are claiming? Will the impact be as broad as some expect and what is the evidence on which to base these assumptions?

What is personalized medicine?

It is ten years since the term 'personalized medicine' was first used in the context that we understand today [7], and the intervening years have seen a dramatic expansion in its prevalence in the scientific community [8] and a widening recognition in the wider population. There is no single universally accepted definition of personalized medicine, but most definitions align with the phrase 'the right drug for the right patient'. It is hard for even the most cynical opponent of personalized medicine to disagree with this sentiment, but in itself, this 'motto' does little to distinguish personalized medicine from well-practiced medicine more generally (no physician would knowingly prescribe the wrong

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medicine). The more comprehensive definition provided by the PCAST report is more helpful and relevant:

'Personalized medicine' refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.

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Simply put, the more specifically we define diseases and the patients that are affected by them, the more able we will be to treat them effectively. Personalized medicine, therefore, is a natural progression of the good clinical practice that has always been the foundation of good healthcare provision and reflects a continuous process of refinement through stratified medicine [9,10]. The crucial difference is primarily the speed of change; the rapid advancement in molecular and particularly genomic technologies that followed the completion of the human genome project has delivered a plethora of new diagnostics and targeted therapies into medical practice. This is reflected by the focus of the PCAST report on genomic-based molecular diagnostics as the most notable area of growth in personalized medicine, and although it acknowledges the contributions from other fields, its recommendation focuses primarily in this area.

The assumption that personalized medicine makes, then, is that our current standard of diagnosis of human diseases and patient responses to both disease and therapeutic intervention are incomplete. One key piece of evidence that supports this premise is the variability in response of patients to standard drug treatments. Although there is considerable variation across different diseases, between 30% and 70% of patients will fail to respond to a drug treatment [11]. Whereas many factors are likely to contribute to these low rates of drug response, including accuracy and completeness of patient adherence to therapy, it seems probable that patient-specific factors such as variation in drug metabolism rates and variation in the nature of the underlying disease are also important contributing factors.

Targeted therapy in cancer – setting the example

The treatment response rates in cancer are amongst the lowest for any major disease, and this, coupled with the now well-established genomic basis of cancer pathology, has long put cancer research in the vanguard of personalized medicine. Oncology has delivered key successes in personalized medicine: the examples provided by Herceptin in breast cancer and Gleevec in chronic myeloid leukaemia (CML) have long carried the mantle for individualized therapy. A humanized monoclonal antibody directed against the extracellular domain of the HER-2 receptor tyrosine kinase, which is amplified in approximately 20% of invasive breast cancers, Herceptin (Trastuzumab) was approved along with a diagnostic test for HER-2 overexpression in 1998. HER-2 amplification was known to have adverse prognostic significance, so as a targeted therapy against this high-risk subgroup, Herceptin has become an important therapy option in both the adjuvant and metastatic

settings [12]. Working in this molecularly defined subset of breast cancer patients, Herceptin has been instrumental in creating an awareness of personalized medicine within the wider community and has come to define personalized medicine for many people. Continuing to build on this success, recent reports have shown the efficacy of Herceptin in a HER-2 positive subset of gastric cancers [13,14].

The discovery of the Philadelphia chromosome, the product of translocation between the long arms of chromosomes 9 and 22, as the hallmark of CML represents the first linkage of a molecular rearrangement with a specific disease [15,16]. When it was later shown that BCR-ABL, the fusion protein created as a result of this translocation, can itself induce a myeloproliferative disorder representative of CML, it confirmed that the translocation is not only diagnostic but also causative of the disease. Gleevec (Imatinib), which was approved in 2001, is an inhibitor of the ABL tyrosine kinase that has become the primary therapeutic intervention for CML [17]. Given the specificity of the Philadelphia chromosome for CML, the translocation is used both diagnostically and therapeutically to monitor response to Gleevec. Like Herceptin before it, Gleevec exemplifies how improved molecular classification of disease not only provides improved diagnostic information but also enables the development of therapies targeted towards these specific disease subsets.

Molecular diagnostics – prognosis and prediction

Pathologically defined disease subsets described by the location of the tumour or the originating cell have been fundamental for medical treatment in cancer for decades. Oestrogen and progesterone receptor status in breast cancer has long been known to predict response to endocrine therapies such as tamoxifen and arguably represent one of the first examples of personalized medicine [18]. The clear molecular differences seen in breast cancer have also lent themselves to genomic profiling, and through transcriptional profiling approaches, several prognostic and predictive assays have been developed. Prominent amongst these is Oncotype Dx, a 21 gene polymerase chain reaction (PCR) panel that predicts tumour recurrence at ten years in ER-positive, node-negative breast cancer patients receiving tamoxifen therapy [19]. Using a statistically defined algorithm, the gene expression profile is used to define a recurrence score that can be used to identify patients who are likely to benefit from additional adjuvant therapy. Patients with low recurrence scores and, therefore, good prognosis are spared the stress and risk of unnecessary therapy, and the healthcare system saves the costs of delivering additional treatment. Oncotype Dx in that sense exemplifies the case for personalized medicine. The assay has been endorsed by both the Association of Clinical Oncologists (ASCO) [20] and the National Comprehensive Cancer Network [21], and the fact that the cost of the test is largely offset by the savings from unnecessary therapy has brought it endorsement from the majority of payer organizations.

Although it is one of the first, and certainly the most successful to date, it is already clear that Oncotype Dx is merely the tip of the iceberg. In breast cancer alone, we have seen the emergence of multi-analyte tests based on techniques as broad as PCR, microarray, immunohistochemistry and fluorescent *in situ* hybridization, amongst others [22]. Genomic Health, the developers of

Oncotype Dx, are expanding the use of their assay in breast cancer, as well as developing similar prognostic tests for colon cancer, prostate cancer, non-small cell lung cancer, renal cancer and melanoma. Most advanced is the prognostic panel for stage II colon cancer, positive clinical data for which were presented at the recent ASCO meeting (http://www.asco.org/ASCOv2/Department%20Content/Communications/Downloads/FINAL_AM_09%20May_14_release.pdf). Again, they are not alone: at the same meeting Agendia presented initial data on the use of their ColoPrint microarray gene panel (they have already launched a breast cancer microarray – Mammarray) for both prognostic and predictive indications. Agendia has also developed a microarray (CupPrint) [23] in the equally competitive area of classification of cancers of unknown primary origin, in which mRNA (Tissue of Origin) [24] and miRNA (miRview mets) [25] classification microarrays also exist.

Recognizing the rapid expansion in the use of these more complex diagnostic tests in prognostic (diagnostic of disease prognosis) and predictive (diagnostic of efficacy or adverse events to a stimulus such as drug) decision making, in July 2007, the FDA released its Draft Guidance document for *in vitro* diagnostic multivariate index assays [26]. In releasing this document, the FDA acknowledged both the growing importance of such tests and its plans for increased regulatory oversight for the development of such complex diagnostics, with clear clinical implications. Although at face value this would seem a positive step in the development of personalized medicine, the planned legislation – which will add to an already complex regulatory situation – has caused much concern within the diagnostic community. Highlighted by PCAST as a potential barrier for the adoption of personalized medicine, the development of a clear and straightforward path to diagnostic approval is needed to maintain momentum in this key area.

Targeted therapy in cancer – keep the pathway intact

Despite the early successes of Herceptin and Gleevec, there was little encouragement for personalized medicine advocates in the area of targeted therapies for many years. Indeed, the failure of key drugs such as AstraZeneca's Iressa (Gefitinib) undermined the rationale. Iressa, an inhibitor of the epidermal growth factor (EGFR) receptor tyrosine kinase that was approved by the FDA in 2003 based on phase II data in non-small cell lung carcinoma (NSCLC), seemed to hold promise for personalized therapy. However, in 2005, its use was restricted to patients already benefiting or those enrolled in clinical studies because of disappointing results in two phase III studies in relapsing or refractory NSCLC [27]. Although Iressa showed benefit in subsets of patients (notably women, Asians and non-smokers), it showed inconsistent response across the broader patient population [28]. Analogous to the situation with Herceptin and HER-2, initially it was hoped that monitoring EGFR expression levels might predict response and serve as a companion diagnostic. However, results to date have been disappointing, and there is no clear link between EGFR expression levels and response to Iressa.

AstraZeneca did not give up on Iressa, however, and they have pursued the efficacy in Asian populations with several large-scale studies in Asia. Following up on some initial results of retrospective analyses showing a possible association between EGFR

mutation status and responsiveness to Iressa [29,30], recent studies have shown a clear link between certain mutations within the EGFR gene and response (http://www.asco.org/ASCOv2/Department%20Content/Communications/Downloads/FINAL_AM_09%20May_14_release.pdf) [31]. On the basis of these data, the Committee for Medicinal Products for Human Use of the EMEA approved Iressa for the treatment of NSCLC with confirmed EGFR mutations in April this year [32].

The data for Iressa are particularly relevant coming on the back of the data generated with two anti-EGFR monoclonal antibody therapies late last year. At the end of 2008, an Oncology Drug Advisory Committee (ODAC) meeting was convened to consider the case for restricting the use of two monoclonal antibodies directed against the EGFR receptor [Erbix (cetuximab) and Vectibix (panitumumab)] [33]. Again, these EGFR-directed therapies showed efficacy in a subset of patients, this time in metastatic colorectal cancer. Again, too, there was no clear correlation between EGFR expression levels and responsiveness to therapy. However, clinical data generated in metastatic colorectal cancer patients have shown that a subset of patients carrying mutations in the *KRAS* oncogene are unresponsive to drug treatment, whereas patients carrying wild-type *KRAS* respond well [34,35]. As with Iressa, a correlation with downstream signalling capability rather than overall expression *per se* was predictive of response to therapy, thus opening up a new paradigm in personalized medicine and moving beyond the direct target expression paradigm set by Herceptin and Gleevec.

The ODAC meeting was also interesting for reasons beyond the science. At the time of the meeting, both Erbix (2004) and Vectibix (2006) were already approved for the treatment of colon cancer by the FDA based on efficacy in unstratified patient populations. The companies, rather than the FDA, wanted to use these additional data to restrict usage to patients shown to harbour wild-type *KRAS*. The FDA was reluctant to agree to restriction of the patient population based on the retrospective nature of the data presented. These extraordinary proceedings are indicative of the sea change that personalized medicine is likely to bring to the pharmaceutical sector. The conflicting requirements of regulators and the payer community make it difficult to define a clear path to drug approval and, ultimately, reimbursement.

Companion diagnostics – where next?

As well as heralding the era of personalized medicine, Herceptin can also take the credit for heralding the advent of companion diagnostics. Approved along with a diagnostic test for HER-2 expression monitoring and a strategy for defining expression levels for inclusion or exclusion of patients from therapy, the Herceptin test set the precedent for other companion diagnostics to follow. Clearly, accurately defining the patients likely to respond to a therapy is as crucially important as the safety and effectiveness of the therapy itself, so clarity about the regulatory requirements around such tests is essential. The drug diagnostic co-development draft guidance document released by the FDA in April 2005 went some way to provide guidance in this area [36], but we still await the publication of a finalized document. The development of companion diagnostics can be both a risky and an expensive business, so if personalized medicine is going to be successful, further clarity regarding the requirements for diagnostic development and

reimbursement are urgently needed. This was echoed in the PCAST report in its recommendation.

Maybe there is an alternative route to delivering personalized healthcare, though. If tumours can be broadly profiled upfront, it might alleviate the need for specific therapy-based companion diagnostics and enable the physician to choose rapidly between all available therapies. This rationale forms the basis for the recent announcements by both Massachusetts General Hospital and the Memorial Sloan-Kettering Cancer Centre to produce comprehensive assessments of somatic mutations at diagnosis for all patients [37]. Specifically, they will look at 110 mutations across 13 cancer-related genes. An even broader approach is taken by California-based biotech company CollabRx, which offers a custom tumour profiling service (<http://collabrx.com/>). These approaches, which are expensive to perform at the moment, will benefit from the rapid advances in genomic technologies and are likely to become cost-effective strategies in the near future. With this information in hand, the physician can choose from the available therapies based on the intactness of the appropriate signalling pathways for that specific tumour. In many ways, this would be a considerable advance in personalized medicine, enabling us to move away from the sometimes controversial binary results of individual companion diagnostics to a more holistic view of therapeutic options. This example plays to the goals of the PCAST report, whereby improved molecular diagnostics is driving improved information gathering and, ultimately, clinical decision making, rather than a restrictive regulatory/reimbursements system.

Beyond oncology

Examples of therapy targeted at specific disease subpopulations have been slow to develop outside of oncology, but they are beginning to appear [38]. Selentry (maraviroc) is the first licensed CCR5 co-receptor antagonist drug that blocks HIV viral uptake into CD4 T cells [39] and represents the clearest example of targeted therapy outside oncology. To gain entry into T cells, the HIV virus interacts with both the CD4 receptor and either CCR5 or CXCR4 co-receptors. Selentry binds to CCR5, thus blocking viral interaction and T-cell entry, but its efficacy is limited to those strains of HIV that use CCR5 rather than CXCR4 as the co-receptor. Testing for CCR5 tropism of the virus, therefore, is essential to determine patients likely to benefit from Selentry treatment, and the drug was approved with a companion diagnostic assay (Trofile).

Although improved disease diagnosis represents one important tenet of personalized medicine, the minimization of adverse events across all diseases represents another [40]. What the drug does to the disease is key to improved efficacy, but what the body does to the drug is key to understanding adverse event monitoring. Given the rare and sporadic nature of many of these events, it is perhaps not surprising to discover that in many cases, genomic-encoded variations account for a significant proportion of these adverse events. Although rare with each drug, the cumulative burden of adverse events on the healthcare system is high. Recent estimates show that more than 5% of hospital admissions are associated with adverse reactions to prescribed drugs [41]. Generally, these genetically linked adverse events can be broken down into two categories: those associated with hypersensitivity reactions to the drug (such as those associated with variants of the HLA

locus, such as seen with carbamazepine [42]) and, more commonly, those associated with impaired or variable metabolism of the drug (associated with variants in genes including cytochrome P450s, dihydropyrimidine dehydrogenase, UDP-glucuronosyltransferase 1A and thiopurine methyltransferase) [38].

Metabolism in the liver by cytochrome P450s represents by far the most common route of drug turnover, and it has long been known that fast- and slow-metabolizing variants in these enzymes can lead to under- and over-dosing of drugs [43]. Recognizing this point, the Roche Amplichip was approved by the FDA to monitor 29 variants in the two most common drug metabolizing P450s: CYP2D6 and CYP2C19 (although this does not include all variants). Known to mediate the metabolism of almost 25% of drugs, adverse events with nearly 30 drugs are known to be related to drug accumulation in patients carrying variants in these two enzymes [44]. In addition, some drugs – tamoxifen being the most prominent example – are delivered in pro-drug form, requiring cytochrome P450 processing to generate the active metabolite. Patients carrying poorly metabolizing variants of CYP2D6 have been shown to produce lower levels of active drug, leading to underdosing and the potential for reduced response [45].

Early this year, an international consortium published their findings on the use of genomic information on the prediction of dose selection for warfarin (coumadin) [46]. Warfarin, prescribed as an anticoagulant, has a very narrow therapeutic range, and there is substantial individual variation in response. Under- or over-dosing with warfarin is the leading cause of hospitalization owing to adverse events worldwide. Much is known about the metabolism of warfarin, and variants in CYP2D9 and VKORC1 are known to influence turnover of the drug. Study results have shown that the prediction of dose selection with a pharmacogenetic algorithm correlated well with empirically determined maintenance doses and outperformed clinical prediction and standard dose estimates. As expected, this was particularly true in the outlier population, whilst patients with common variants of the metabolizing enzymes fell within the range of standard dosing.

The FDA, recognizing the clinical value of these findings, has been updating drug labels to include such genetic information where compelling data exists. The labels for both tamoxifen (2006) and warfarin (2007), for example, have been reviewed and changed in recent years, but in both cases, the FDA did not make testing a requirement on prescribing or define a process for interpreting results [47]. Similarly, a review of the available warfarin data has been completed by the Centres for Medicare and Medicaid, and although they acknowledge the scientific basis of the findings, their proposed decision (published in May this year) is not to cover genetic testing for warfarin dosing [48]. In many ways, the examples of tamoxifen and warfarin exemplify the dilemma that will face healthcare systems going forward. The technical evidence is strong: personalized medicine has delivered tools that can predict dosing better than current best practice. But how should one balance physician time, patient inconvenience and reimbursement costs of a molecular test? How much better does the test need to be before it becomes cost-effective, and how much time does it need to save? Difficult questions, indeed. Again, PCAST recognized this difficulty; their recommendations highlight the need for a clearly thought-out process to tease out the potential

benefits of the new personalized medicine paradigm and strike to the heart of the problem that we will increasingly face.

Concluding remarks

After a slow start, progress on the path to personalized medicine is gathering pace. There are a growing number of examples in which personalized medicine is influencing clinical decisions and helping shape healthcare provision. Progress in oncology is rapid and likely to continue apace. Successes outside of oncology are still limited, though, and only time will tell how broadly applicable

personalized medicine will become. Updating the regulatory and legislative framework to remove barriers to the development of molecular diagnostics, as PCAST suggests, will be essential to allow personalized medicine every chance to flourish. There are many that remain rightly sceptical regarding whether personalized medicine will ever be able to deliver on its promise [49,50] and, specifically, whether the argument for the adoption of molecular diagnostics will ever be economically viable [51]. Either way, the personalized medicine experiment is now well underway, and the next few years will see whether the faith was justified.

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