Over the last two decades, treatment outcomes have improved markedly for a number of cancer types, including breast cancer, lung cancer and melanoma. Some of these improvements can be attributed to the steady development of new treatments. However, what has been very different in this period is the introduction of a different approach to healthcare management. Precision medicine is a strategy of customizing health management to individual predisposition and condition subtype, instead of the conventional approach of applying a standardized management. In oncology, a move towards precision medicine has been motivated by an accumulating number of paradigms that have demonstrated its significant health and financial value. However, shifting to this type of medicine entails many disruptions to current research and clinical practices, including the introduction of new disciplines and structures, new levels of multidisciplinary co-operation, new approaches to health regulation and economics and the generation of new information on inter-population clinical and molecular features. In this article, we look back at key events in precision oncology to relate the motivation behind the shift and understand the upcoming issues in realizing the immense potential of precision medicine.

Lessons learnt from the HER2 story: personalizing breast cancer treatment

In oncology, evidence and motivation for a shift towards precision medicine have been accumulating over the last two decades (Figure 1 and Table 1). The paradigm commonly attributed to initiating the consideration of precision oncology has been the application of trastuzumab (Herclon®/Herceptin®) to breast cancer patients with overexpression of the human epidermal growth factor receptor 2 (HER2) protein. HER2 is a receptor on the cell surface that generates signals for numerous tumour-promoting functions when activated and is overexpressed in a subset of breast cancers. Trastuzumab is a humanized antibody designed to bind to HER2 and block its signalling, and activate the immune system. During the development of trastuzumab, it was observed that trastuzumab elicited tumour reduction in only approximately 10% of cases of all breast cancers, but was active in approximately 50% of cases of tumours with HER2 overexpression. Applied to all breast cancers, trastuzumab would have struggled to gain approval from regulatory authorities. Hence a difficult decision was made to restrict application of trastuzumab to only cases with tumours overexpressing HER2, forgoing the approximately 80% of breast tumours that did not overexpress HER2. At that time, this decision was a radical departure from traditional drug development approaches geared to blockbuster ‘one-for-all’ drugs. Nonetheless, analysis has indicated that the decision saved US$35 million in clinical trial costs, generated US$2.5 billion and made the drug accessible to 120 000 patients through acceleration of product approval. The financial and health advantage obtained – as well as the precedent set – has started the ball rolling for far-reaching changes in the way academic, industry and regulatory authorities approach drug development.
Rediscovering gefitinib: EGFR mutations and NSCLC

Following trastuzumab, another key paradigm that added further motivation and instruction on precision medicine was the development of the inhibitors against epidermal growth factor receptor (EGFR). EGFR is a cell receptor that belongs to the same family of proteins as HER2, and is overexpressed in a different spectrum of cancers. Gefitinib (Iressa®) is a small molecule designed to bind to and inhibit the signalling domain of EGFR. Gefinitib was initially approved for non-small-cell lung cancer (NSCLC) in the USA in 2003 based on a ‘one-for-all’ approach, but the US Food and Drug Administration (FDA) withdrew its approval 2 years later based on clinical trial data indicating that it did not improve survival1. In subgroup analysis, East Asians were observed to have a higher tendency to respond, although the value of this was not apparent at that time. In 2004, some insight into this phenomenon was revealed by the discovery of mutations in the DNA encoding the signalling domain of EGFR in NSCLC. Gefinitib was approved for non-small-cell lung cancer with EGFR mutation in 2004. However, the trial also revealed that if patients with tumours without EGFR mutations were treated with gefitinib, they were likely to have a worse survival. With these results came a legal impetus to practise precision medicine, and avoid the potential implication of negligence in providing gefitinib without knowledge of EGFR mutation status. Hence, in addition to providing strong reinforcement of the value of precision medicine, gefitinib proved to be a key motivator of a large majority that were resistant or not informed of the need to practise precision medicine.
Drug repurposing in precision medicine: a complex but valuable approach

After trastuzumab and gefitinib, taking a precision medicine approach to introducing new drugs transitioned from a rare to a common consideration. With every development, new lessons were learnt and further motivation was gained. The detection of \textit{KRAS} mutations in colorectal tumours to select against treatment with cetuximab (Erbitux\textsuperscript{a}, an anti-\textit{EGFR} antibody) set a precedent for avoidance of a treatment based on a biomarker\textsuperscript{b}. The \textit{BRAF} protein is involved in directing cell growth and mutations in its gene have been linked with a number of cancers including melanoma. Applying \textit{BRAF} inhibitors, such as vemurafenib (Zelboraf\textsuperscript{c}), to melanoma patients with \textit{BRAF} mutations in their tumours became another success of precision medicine. However, this strategy was not effective for colorectal tumours, cautioning against the assumption that drug and biomarker relationships are valid across all conditions. Functional investigations revealed that the differences in activity between melanoma and colorectal cancer were due to the presence of different cofactors that influence inhibition and signalling in the cancer types\textsuperscript{d}, highlighting the need for a strong scientific understanding of cancer biochemistry when developing precision oncology drugs.

Another key precedent was set by identification of aberrant fusions of the DNA encoding the \textit{EML4} and \textit{ALK} (anaplastic lymphoma receptor tyrosine kinase) genes in NSCLC, and the application of crizotinib (Xalkori\textsuperscript{e}) (an inhibitor of the \textit{ALK} family of proteins, which play a role in brain and neuron development) to these cancers. These fusions were relatively rare (~5% of NSCLC) and developing a treatment for them would have been previously considered unviable based on a ‘one-for-all’ approach\textsuperscript{f}. However, by applying a precision medicine approach, outstanding response rates (over 65%) were achieved, which led to an expedited regulatory approval in the interests of providing access. The time from idea to approval was 3 years for crizotinib compared with 13 years for trastuzumab, highlighting the benefits of precision medicine to drug development. Part of the reason for the shortened time was that crizotinib had previously been tested for another indication (anaplastic large-cell lymphoma). However, that also was a valuable motivational aspect of this paradigm, as it demonstrated that a drug can be ‘repurposed’ for a rare indication and achieve expedited approval through a precision medicine approach.

Precision medicine meets the genomic age

Developing at the same time was the technology of next-generation sequencing (NGS). Based on massively parallel sequencing of DNA and complex data processing, NGS enables simultaneous analysis of multiple aberrations in a single analytical session from a single sample. As little as a few genes (targeted NGS, 1–100 thousand bases of DNA) to up to all 28,000 plus protein-coding genes (exome, ~30 million bases) or all human DNA (‘whole genome’, ~3 billion bases of DNA) can be sequenced by NGS, with relevant scales of expense. Beginning in the late 2000s, NGS was used to characterize the range of aberrations present in human cancers, through large consortia such as The Cancer Genome Atlas (TCGA, 20,000 biospecimens of 33 cancer types), the International Cancer Genome Consortium (ICGC, 15,000 cancer genomes spanning 66 projects), as well as many independent studies. The NGS efforts accelerated the identification of aberrations suitable for matching with drugs and precision medicine; but they also surreptitiously introduced a new phase and complexity to precision medicine. NSCLC soon appeared as a conglomerate of tumours differing in aberrations in \textit{EGFR}, \textit{KRAS}, \textit{ALK}, \textit{ROS}, \textit{RET}, \textit{HER2}, \textit{BRAF}, \textit{MET}, \textit{AKT1}, \textit{MAP2K1} and \textit{PIK3CA}, and with each aberration pointing to a different treatment. This obliged a transition for precision medicine from treatment selection based on a single genetic aberration to a system of triage involving many treatment options and requiring multi-marker analysis.

This transition has proven to be difficult to achieve due to the new technology (e.g. clinical NGS), new disciplines (e.g. medical bioinformatics) and new level of multi-disciplinary collaboration required for its execution. Nonetheless, a number of centres have been able to organize themselves and have embarked on testing the feasibility and value of a multi-marker precision medicine approach. The studies include the CUSTOM trial on lung and other chest cancers from the USA; the SHIVA\textsuperscript{a} and MOSCATO\textsuperscript{g} trials on multiple cancer types from France; the IMPACT and COMPACT trials on NSCLC, breast, colorectal and ovarian cancer from Toronto, Canada\textsuperscript{h}; the Phase I programme from the MD Anderson Cancer Centre, USA\textsuperscript{i}; and the WINHER trial on all cancers spanning France, Spain, Israel, Canada and the USA\textsuperscript{j}. The US National Cancer Institute is expected to tap on a proposed US$70 million investment in precision medicine\textsuperscript{k} to scale up efforts for its NCI-MATCH trial\textsuperscript{l}. This trial aims to screen approximately 3000 patients across approximately 2400 sites and enrol 1000 patients into various treatment arms comprising more than 20 drugs. The UK government has committed to providing £300 million for the 100,000 Genomes Project that will be completed by the end of 2017 and will include 50,000 cancer genomes (http://www.genomicsengland.co.uk/). By 2030, it is projected that Asia will bear nearly half of the world’s cancer burden (10.7 of 23.6 million new cases)\textsuperscript{m}. Hence Asia is also actively investigating precision oncology, including the VIKTORY trial (ClinicalTrials.gov NCT02299648) in South Korea, the GI-SCREEN study in Japan\textsuperscript{n} and our very own IMAC trial (NCT02078544) in Singapore, which has been running for 2 years.

Recently, the results of some of these trials have started to be reported. The CUSTOM trial enrolled 647 patients with lung and chest cancers into multiple, parallel Phase 2 trials, based on the presence of mutations in 11 genes linked to 15 available treatments (including standard of care)\textsuperscript{o}. The major experience reported from this trial, however, was the difficulty in assigning patients to the treatment arms, due to the inadequacy of laboratory testing and the rarity of some aberrations, among other enrolment issues. Nonetheless, a 60% response rate for patients with \textit{EGFR} mutations was observed for erlotinib (Tarceva\textsuperscript{p}) (an \textit{EGFR} inhibitor) within this trial design, supporting that successful triaging could be achieved within this future system.

An October 2015 report on the SHIVA trial indicated that there was no significant difference in the progression-free survival of 195 patients with advanced cancers enrolled into either standard-of-care treatment (median 2.0 months) or 10 treatment arms based on mutations in three molecular pathways (2.3 months)\textsuperscript{q}. Although not supportive, many have taken this trial to be useful in instructing on the finer requirements of precision medicine. The activity of many regimen assignments was unknown in many cases,
and the results may have been more supportive if focused on validated relationships. The authors also offered that a combination treatment strategy may have been better to overcome drug resistance associated with the single agent treatment approach used in this study.

The path forward for precision medicine

Looking ahead, it would seem inevitable that precision medicine becomes embedded into the framework of healthcare based on the evidence and reasoning that has accumulated over the last two decades. However, the recent trial results have highlighted that there remains much work to do in order for it to be an efficient process and one that brings true value to healthcare.

Throughout the last two decades, a recurring issue has been the preparedness of molecular diagnostics to step up and take the major role thrust upon it by precision medicine. During the development of trastuzumab, a lack of standardization and variability in the inter-observer interpretation meant that reliable assessment of HER2 overexpression took close to 5 years and numerous international consortia to achieve. During the development of gefitinib, arguments were raised that it could be faster to observe responsiveness to treatment than wait for the EGFR test results. Today, the molecular diagnostics community is grappling with providing multi-marker testing, with the capability only available in a few advanced centres. Part of the problem has been that the technology behind molecular diagnostics has predominantly been developed by laboratory scientists, but is deployed in the health system by pathologists, and some of the knowledgebase and experience is lost in the handover.

In addition, the rise of relevant technology such as NGS has been so rapid that many practitioners and regulators are missing the relevant foundational knowledge (e.g. informatics) or relevant experience in their past training. In addition, the new technology requires new infrastructure (e.g. computer servers in pathology) and the development of new cost models and regulatory frameworks that have never before existed. There are also relationship issues between physicians and the molecular diagnostic community, which suddenly has a more prominent role in determining treatment selection.

Resolution of these issues will reduce a large bottleneck in the progress of precision medicine.

Another issue that is reflected in the recent trial reports is the limited knowledge of appropriate treatment matches to biomarkers, in particular DNA variants. Biomarkers can be predictive of sensitivity, or resistance, or have no relationship at all to treatments, and for precision, treatment relationships for each variant need to be known. In some cases, the biomarkers can also be relevant in the general population as well as being specific to tumours in other cases. Examples of this are certain BRCA1/BRCA2 DNA variants, which can be predictive of breast cancer risk and/or confer sensitivity to treatment with poly(ADPribose) polymerase (PARP) inhibitors. Biomarkers can also vary in prevalence between populations (e.g. EGFR mutations), and they can also vary in significance according to context (e.g. BRAF mutations). Predictive algorithms are constantly being developed, but is becoming more apparent that annotation of biomarkers linked to real-life population and clinical phenotypes is required.

Given the 3 billion bases in human DNA, in addition to the infinite number of non-DNA biomarkers, a degree of international co-operation to develop relevant knowledge bases is clearly needed.

There are many other issues that would be too long to describe in detail. Confidentiality issues relating to the annotation of the human population and the implications of misinterpretation and incidental findings all loom large as quality management, ethics, legal and regulatory issues. The limited amount of active treatment options has frequently been cited as an impediment to precision medicine. Maintaining all of the treatment options for the multitude of rare indications, as well as co-ordinating treatments from different providers, are related quandaries that have also been generated by precision medicine. Last, but not the least, are the new cost models that need to be generated for precision medicine, for which there is much unfamiliarity, much concern about new test costs and a paucity of suitable reference data.

All in all, it is evident that many challenges lie ahead for precision medicine. In the end, perhaps the most important conclusion to draw from the history and recent results in precision medicine is the undeniable need for multi-disciplinary collaboration for its execution. With precision medicine here comes a new requirement for novel infrastructure and diverse skills, experience and contributions that only collaboration can meet (Figure 2). This includes the functional co-operation of physicians, pathologists, laboratory scientists, medical bioinformaticians, quality managers, drug developers and fundamental biologists from academia, healthcare and industry. Should this provision occur, the future will look bright for individual health and well-being.

Figure 2. A framework of the specialists (inner circle) and infrastructure (outer circle) needed for successful implementation of precision medicine. The diverse domain expertise and skills required for precision medicine obliges that new disciplines and structures become stakeholders in clinical care. Integral to the framework is the multi-disciplinary collaboration and respect of all the components in the ecosystem.
References


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