

Personalised cancer care: fad or future?

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Introduction

The impact of cancer care on individuals and Australian society is hard to ignore. In 2010, 114,000 Australians were diagnosed with cancer, and an estimated 1 in 2 Australians will be affected by the disease by age 85¹. Cancer care already consumes 3.8 billion dollars per year in Australia, making up 7.2% of the annual health budget¹. Therefore, any change in our approach to cancer care will have vast implications for the health of individuals and populations, as well as our economy.

Traditionally, our approach to cancer has relied on morphological and histological classifications to guide the use of chemotherapy, radiotherapy and surgery. However, for many cancers, this classification system correlates poorly with treatment response, prognosis and clinical outcomes². As data from The Cancer Genome Atlas (TCGA)³ and the International Cancer Genome Consortium (ICGC)⁴ becomes available, we are able to uncover the molecular basis of cancer's clinical variability. This has shown that even within a cancer subtype, the mutations driving oncogenesis are diverse. Furthermore, individual genetic polymorphisms can now be correlated with drug responsiveness and toxicities^{5, 6}. The more we learn about the molecular basis of carcinogenesis, the more the traditional paradigm of chemotherapeutic cocktails for cancers classified by histological and morphological features appears increasingly inadequate. In response, the hope for personalised medicine has been growing.

The Promise of Personalised Cancer Care

The US National Cancer Institute defines personalised medicine as “ a form of medicine that uses information about a person's genes, proteins and environment to prevent, diagnose and treat disease.”⁷ In other words, personalised cancer care strives for sufficient understanding of the molecular basis of disease to tailor prevention and drug therapy to individuals and populations. This could not be more relevant to cancer, which may be conceived as the ultimate betrayal –self turning against the self.

The ability of personalised cancer care to improve outcomes is historically linked to the development of imatinib for chronic myeloid leukemia (CML) and trastuzumab for breast cancer. CML was a historically fatal disease, with a chronic phase of 5 years before rapid acceleration towards death⁸. However, in 1998, imatinib was specifically created to inhibit the constitutively active tyrosine kinase resulting from a translocation between chromosomes 9 and 22. Ultimately, this drug has proven

to be so effective that patients with CML now have mortality rates comparable to those of the general population⁹. The other success story is that of trastuzumab for patients with Her-2 positive breast cancer. In the earliest studies, Slamon demonstrated that in every conceivable area of response, patients treated with the Her-2 antagonist trastuzumab had a measureable benefit over traditional therapies^{10, 11}.

With the advent of these drugs, personalised medicine for the future of cancer care began to take shape. In imatinib and trastuzumab, the medical community realized Paul Ehrlich's dream of a "magic bullet", a drug with the capacity to kill cancer cells but with enough specificity to spare the normal cells surrounding them¹². Since the adoption of these drugs, additional targeted therapies have gradually strengthened oncologists' arsenal¹³⁻¹⁷. At present, 28 targeted molecular therapies have been approved by the FDA for use in a range of cancers¹⁸, and numerous others are in clinical development. These targeted therapies offer improved outcomes compared to traditional treatments. In many ways, personalised medicine and its promises of improved cancer care have already become a reality.

However, it remains unclear whether personalised medicine will provide oncology with the panacea it has long sought - the silver bullet to end the war that Nixon declared on cancer in 1971. While the demonstrated benefits of tailored therapies over traditional chemotherapy point to personalised medicine as the logical way forward, the question of what shape this future will take is less clear. Widespread implementation of personalised cancer presents some challenges. These include: 1) overcoming drug resistance; 2) developing valid drug targets and establishing predictive biomarkers; 3) delivering personalised solutions for both majority and minority populations; and 4) ensuring that future doctors are adequately trained to work in this new era. If we are unable to solve these challenges, personalised cancer care risks becoming a fad rather than the future.

The Challenge of Resistance

Just as resistance develops to traditional chemotherapeutic agents, similar patterns are emerging for personalised targeted therapies. For patients with BRAF positive melanoma treated with PLX4032, almost all patients eventually developed resistance¹⁵. In patients treated with temozolamide for glioblastoma multiforme, progression free survival averages 10.3 months before treatment failure and resistance develop¹⁴. In those given erlotinib and gefitinib for non-small cell lung cancer (NSCLC), as well as with the targeted agent bevacizumab, the overall clinical benefit has been minimal, and all patients eventually develop resistance^{16, 17, 19, 20}. Even with the most successful personalised

treatments available today, such as imatinib for CML, up to 20% of patients have either inadequate initial response, intolerable side effects or eventually develop drug resistance²¹⁻²³. The mechanisms underlying the emergence of resistance are diverse²⁴. Some patients develop mutations at drug binding sites²¹⁻²³, others develop downstream mutations that may lead to reactivation of oncogenic potential²⁵⁻²⁷. Others yet may have parallel pathway activation^{25, 26, 28} or feedback upregulation of the initial target²⁹. Therefore, for some individuals, personalised therapies risk becoming personalised failures³⁰.

As our understanding of cancer deepens and we develop more effective drugs, cancer responds with similar developments; novel mutations to render our drugs ineffective. Indeed, the very nature of cancer is that of mutation – nature’s most effective mechanism for developing new solutions, or in the case of cancer, new betrayals. As so eloquently stated by Siddhartha Mukherjee, “This is our predicament in cancer: we are forced to keep running merely to keep still”³¹.

If the clinical benefits of personalised therapies are to be sustained, we must develop new solutions to resistance. To help identify patients with primary resistance, one possibility is to develop biomarkers, biological molecules found in fluids and tissues that can predict likely response and resistance prior to initiation of therapy³². For patients acquiring resistance during therapy, novel treatments may be required, such as those used in patients with CML who developed resistance to imatinib^{33, 34}. Another approach may be to use cocktail therapies similar to those adopted for chemotherapy and antiretroviral therapy. Finally, applying our understanding of the mechanisms of resistance may lead to the development of drugs with reduced vulnerabilities to resistance. Ultimately, investing in solutions to overcome resistance is required if personalised medicine is to reach its full potential.

The Challenge of Drug Development

Delivering targeted therapies with reduced toxicities depends on our ability to identify patients likely to respond to treatment. As previously discussed, biomarkers have been proposed for this purpose. However, while many new therapies are reaching the market in record time, the associated biomarker tests have either lagged behind or have not been independently reviewed for accuracy and reliability³⁵. Even for cases of already established biomarkers, such as Her-2 for trastuzumab, 20% of testing has been reported to be inaccurate, exposing patients to possible toxicities without benefit³⁶. In another example, the initial phase III studies of gefitinib for treatment of NSCLC failed to reveal any clinical benefit as biomarkers for detecting activating mutations in epidermal growth factor receptor

(EGFR) had not yet been developed^{37, 38}. As we address the challenge of identifying drug targets, these examples clearly illustrate the importance of developing and validating biomarker assays in tandem.

With the human genome as well as the exomes of 74 cancers already decoded³⁹, identifying suitable drug targets from this data presents another challenge. Developing successful drugs depends on uncovering oncogenic mutations with a clear and substantial causal relationship to cancer. Imatinib was a clinical success in part because the 9:22 chromosomal translocation is found in almost all patients with CML. However, one concern is that such highly conserved mutations may not be found in all cancers. At present, 72 genome wide association studies (GWAS) examining mutations driving cancer can be found in the NIH GWAS database⁴⁰. The risks uncovered by these studies have been modest. For example, a GWAS in breast cancer identified several single allele mutations, but each had odds ratios less than 1.3⁴¹, making them unlikely drug targets. Additional studies have revealed that advanced cancers harbour on average 30-80 mutations³⁹, and it is initially unclear which of these contribute to oncogenic potential. Taken together, these findings highlight the difficulties in identification meaningful drug targets.

Fortunately, possible solutions to these problems are gradually emerging. Perhaps the most elegant solution lies in finding unifying pathways whose derangements are conserved across a wide range of cancers. An idea pioneered by Bert Vogelstein, his research has revealed that the multitude of mutations can be reduced to on average 13 pathways that are deranged in any single cancer³⁹. Even more importantly, these mutated pathways are also conserved between different types of cancer. By reducing the number of possible drug targets from up to 80 mutations per individual cancer to 13 key pathways for all cancer types, Vogelstein has provided the medical community with a manageable goal for future drug development.

The Challenge of Equality

Emerging research indicates that race and ethnicity independently influence survival outcomes and treatment response for some cancers, even after adequately accounting for socioeconomic and treatment differences⁴²⁻⁴⁶. These disparities in outcome may be due to differences in the mutations driving oncogenesis^{42, 47-49}, as well as difference in drug-metabolizing enzymes among racial groups^{42, 50}. Therefore, in order to develop personalised cancer treatments for all, studies must encompass a wide range of racial and ethnic backgrounds. This is particularly important in the Australian context,

where significant disparities in cancer care already exist between indigenous and non-indigenous Australians.

Indigenous Australians fare worse with respect to survival across a broad range of cancer subtypes⁵¹⁻⁵⁵. Aboriginals are already less likely to receive specific cancer treatments, including surgery, radiotherapy and chemotherapy⁵¹. Even when fully accounting for later stage of diagnosis, remote location, language and type of treatments received, almost no studies have been able to fully explain the survival disparities between indigenous and non-indigenous Australians⁵³. Such disparities in outcomes may in part be explained by differences in underlying mutations and pharmacogenomics in Aboriginal populations compared to other Australians. And yet, we can only speculate as a search of the literature to date failed to identify a single article examining difference in cancer genetics and metabolism of cancer drugs in Aboriginal Australians.

For indigenous Australians, other ethnic minorities and people from developing countries, the promises of personalised medicine appear in stark contrast to the persistent global health disparities they face⁵⁶. As personalised medicine delivers for some, it raises important questions about health equality. Will personalised medicine reduce health disparities between the developing and developed world, or only increase the growing divide? Will basic research and clinical trials include unique racial groups such as Aboriginal Australians? Even if effective personalised therapies are available for minority groups such as Aboriginals, how will they access this care when they are already struggling to access currently available services? Without adequately addressing these issues, the potential of personalised cancer care will not be equitably distributed among Australia's population.

The Challenge of Medical Education

Widespread implementation of personalised medicine in clinical practice will require a team approach involving clinicians, scientists, computer experts and biostatisticians². Furthermore, if personalised cancer care improves long term outcomes as promised, the number of cancer survivors requiring follow up and management will also increase, and delivery of this service will fall on present and future oncologists, those planning careers as general practitioners as well as other health care professionals.

Delivery of personalised cancer care will not only involve rolling out the treatments previously discussed, but also preventative services for those found to harbour at risk mutations detected through

genetic testing. As the costs of personal genetic testing become more affordable, with companies in the US already offering these services, it is only a matter of time before patients begin asking their general practitioners to interpret these tests. And yet, when faced with interpreting information about specific genetic mutations, many GPs have historically been ill-prepared. In one study, one-third of physicians incorrectly interpreted the results of a single-gene test for colorectal cancer susceptibility⁵⁷.

To deliver personalised cancer care for the diagnosis, treatment and prevention of cancer, both current and future oncologists, general practitioners, physicians and surgeons require increased knowledge and understanding of molecular biology, bioinformatics and genetics. We must then ask: are our medical schools providing us with the necessary tools to practice in this new era? As I near the end of my medical training, I personally feel ill equipped to interpret the vast array of genetic material currently available. A study of Canadian and US medical schools found that only 11% provided practical training in medical genetics as part of their curriculums⁵⁸. And yet, if personalised medicine is to become the future of cancer care, medical schools must rise to the challenge of providing adequate training in personalised therapies so we can meet the challenges of delivering appropriate personalised cancer care for all Australians. To achieve these goals, medical students will require clear learning objectives and basic competencies⁵⁹. These may include:

1. Understanding the molecular and genetic basis of oncogenesis
2. Learning to interpret GWAS and single allele tests and applying the results to clinical practice
3. Identifying situations where genetic testing will benefit patient care
4. Incorporating genetic information into cancer prevention
5. Appreciating the ethical implications of genomic testing for individuals and families

Conclusion

For the 114,000 or more Australians¹, as well as the millions of others around the world who will be given a diagnosis of cancer in 2011, their battles will be deeply personal. The knowledge we have gained from the genomic revolution will offer some of them new options for the prevention, diagnosis and treatment of their cancer based upon their unique genes, proteins and environment.

However, to fully realise the benefits of personalised cancer care, we must solve the significant challenges that lie before us. These include overcoming drug resistance, developing novel drugs, ensuring equal access to diverse ethnic and socioeconomic groups and investing in future doctors to

ensure they are equipped to deliver the benefits of personalised cancer care. Investing in solutions to these challenges will help turn a promising idea into the future of cancer care.

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