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Editors' View

Adding the 'medicines' back into personalized medicine to improve cancer treatment outcomes

Jennifer H. Martin,[1,2] Elizabeth Phillips,[3,4] David Thomas,[5,6] & Andrew A. Somogyi,[7,8]

[1]School of Medicine and Public Health, University of Newcastle, New South Wales, Australia, [2]The University of Queensland Diamantina Institute, 37 Kent St, Woollongabba Queensland, [3]Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA, [4]Institute for Immunology and Infectious Diseases, Murdoch University, Murdoch, Western, Australia, [5]Garvan Institute of Medical Research, The Kinghorn Cancer Centre, 370 Victoria Street, Darlinghurst, NSW 2010, [6]St Vincent's Clinical School, Faculty of Medicine, University of New South Wales, [7]Discipline of Pharmacology, Faculty of Health Sciences, University of Adelaide, Adelaide, 5001 and [8]Department of Clinical Pharmacology, Royal Adelaide Hospital, Adelaide, Australia

The excitement surrounding the newly redefined concept of 'Personalized medicine' was ignited in the Wall Street Journal in 1999. This heralded a 'New Era of Personalized Medicine' to 'target drugs for each unique genetic profile' [1], spurred on by an era of apparently targeted therapies. Today, personalized medicine has been redefined to 'Precision medicine' to incorporate genomics and aimed at developing new targets, treatments and optimized therapy. Ideally, the clinician's concept of personalized medicine is about the right drug, dose, patient and time. Additionally it involves basic principles of pharmacological and clinical medicine. Although personalized medicine embodies the culture of clinical pharmacology, this Editorial alerts to the paradox that lack of the input of clinical pharmacology into personalized medicine has led to incomplete translation of genomic data into the optimal choice and application of cancer drugs and the funding decisions of public access to therapies.

The task of matching diagnosis to treatment strategy for each individual's molecular makeup is exemplified in oncology, but is more challenging than envisioned as the science remains in evolution. Tumours are heterogeneous and their genetic expression varies over a given treatment period, and many gene mutations do not affect protein expression or activity. Therefore making long term clinical decisions based on the genetic readout taken from a tumour at diagnosis has major limitations. Even if this approach did enable the right drug, dose and time, their integration with patient characteristics and concomitant therapies is not the province of tumour genetics alone.

There have been similar challenges in using human germline pharmacogenomics to guide therapy. In particular, the ability to generate information has exceeded the ability to provide sound evidence and reports that can be interpreted and acted upon by doctors. Even though private companies can generate individual drug genetic information with a potential impact on drug therapy [2], the clinical information and decision support along with the genetic information is typically either absent or inadequate. This leaves the treating physician struggling to make any suggested drug or dosing recommendations.

Yet genetic tests of either the drug or a tumour are exciting and innovative and should be able to predict drug responders better than current methods. Patient benefits have occurred with haematological cancers [3] and some solid cancers with well-defined single mutations [4, 5]. But in practice, we need evidence that treating people using a genetic algorithm alone, in populations vastly different and more complex to the clinical trial setting, benefits the patient at hand. This is of particular importance as some people benefit from these therapies even without the genetic mutation, and many patients with the genetic mutation do not respond [6]. The evidence is only accumulating now, although the drugs have been available and often taxpayer funded for many years at a huge financial cost. The corollary is that other patients are denied access to some of these very expensive drugs by payers trying to reduce costs by 'targeting' an apparently uncertain outcome biomarker [7].

Major funding agencies currently undersell the rationale for integration of pharmacology into the 'precision medicine' framework. Moreover, the infrastructure to support clinical scientists and clinicians is absent. Cross disciplinary collaboration of clinicians with drug specialists and scientists [8] is an essential next step in improving

health outcomes in cancer drug treatment and should be supported by research and policy bodies.

For the translation of 'omics'-based tests from discovery to health care, the process must entail more than a focus on tumour genetics alone. What is needed is a comprehensive adaptive and iterative process using phenotype data, responding to new evidence, and with health outcomes (not simply genetic testing) as the overarching focus. There has been criticism that the personalized medicine and tumour genetics bandwagon has used irrational appeals to drive national and European policy makers to ensure continued priority funding of this area [1, 9]. Although the era of precision medicine is about a decade old, evidence still needs to be obtained on improvements in health outcomes (i.e. survival phase IV data). These data are usually not available inside of the clinical trial setting, as patients in the control group are usually given the option of swapping onto the active treatment group, therefore forever preventing knowledge regarding the actual comparative benefit or toxicity to standard care [10].

There are several issues that need addressing in this field. Firstly, the precision medicine model needs to be something that is scalable to the population at large and not just available in specialty settings. We need a mechanism to fund and educate professionals to obtain the necessary skillset required to support translation and evaluation. The key stakeholders are not just the pharmaceutical industry, geneticists and medical oncologists, but also those delivering cancer care (including radiation oncologists and cancer surgeons), clinical pharmacologists, the public (including taxpayers and patient support groups), regulatory bodies (including collection of adverse event data), clinical pharmacists, epidemiologists and laboratory specialists.

Considerable resource has been built to develop 'omics' as a diagnostic tool for disease identification and stratification but this represents one small part of the 'translation into healthcare' – and more is needed to create a translational pathway for the future. In particular there are many 'omic' issues surrounding the discovery and therapeutic use of small and large molecular drugs that would significantly benefit from clinical pharmacology expertise and input in order to provide rational drug and dosing guidance [11].

Compounding these problems of integration of omics has been the sometimes ill-designed and expensive trials, which can have flow on effects in excessive drug prices. For example when using observational data, comparison with placebo [12] is unknown, delivering uncertainties to the estimation of cost for a particular benefit. Drug prices are usually developed based on a model where drug target efficacy is assumed to be the same in the real world setting [13]. The commonly used design of crossing over on progression also invariably hinders measurement of efficacy. For example, examining whether adding trametinib, a MEK inhibitor, to dabrafenib, a BRAF inhibitor would improve progression free survival in melanoma suggested that patients receiving dabrafenib alone progressed a few months before those on dual therapy and were allowed to crossover [11]. Nevertheless, overall mortality curves were the same. More difficult is the lack of ability to provide clinical interpretation of the initial progression data. Interestingly this combination was also initially advocated to reduce the side effects of using the dabrafenib alone. However 60% of patients taking the combination developed fever, compared with 16-26% on dabrafenib alone [14].

It is now increasingly clear that the relationship between a specific gene mutation and the phenotype is much more complex than originally appreciated. Clinical pharmacology can study how a specific individual with a set of pharmacokinetic, pharmacodynamic and pharmacogenetic alterations is likely to respond, compared with another individual with the same mutation but different pharmacological characteristics. Within its realm are also variability in drug absorption, tissue uptake/efflux and metabolism and activity across body sites, including tumour cells. This is quite different from having a tumour mutation and a protein that blocks that gene and assuming that it does all of a) reach the plasma compartment, b) cross into the tumour site at a known concentration and speed and c) have activity in the cell.

We need to also take into account that translation into clinical benefit may be harder than originally expected. Even for a relatively simple translational success such as *HLA-B*5701* screening to prevent abacavir hypersensitivity, the pathway from gene discovery to clinical validation and translation was 6 years [15, 16].

Finally much of the improvement in cancer outcomes to date has been due to early detection and prevention campaigns [17], optimizing the use of currently available chemotherapy [18], radiation and surgical techniques [19, 20], together with improved imaging and pathology toolkits. The creation of true precision medicine in the future will include the integration of genomics and other personalized medicine approaches into one programme. Refocusing of health systems and health service delivery will be necessary to ensure that everyone, regardless of the type or location of cancer, has access to high quality treatment and care. Government proposals to support the precision medicine model should focus not only on potential scientific approaches but should be supported by real evidence that will translate into better outcomes in cancer patients. Personalized multidisciplinary approaches should foster close collaboration, cross-discussion and on-going dialogue between relevant sub-specialists, industry, health funding and regulatory bodies in the interpretation of genetic-guided choice of therapy. In particular these stakeholders should have

input into pre- and post-marketing studies to define their efficacy, safety and effectiveness. Clinical pharmacologists can play a major driving role in the model of personalized medicine to improve cancer treatment outcomes.

Competing Interests

There are no competing interests to declare.

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