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Cancer 2015: a longitudinal whole-of-system study of genomic cancer medicine

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Genomic cancer medicine promises revolutionary change in oncology. The impacts of 'personalized medicine', based upon a molecular classification of cancer and linked to targeted therapies, will extend from individual patient outcomes to the health economy at large. To address the 'whole-of-system' impact of genomic cancer medicine, we have established a prospective cohort of patients with newly diagnosed cancer in the state of Victoria, Australia, about whom we have collected a broad range of clinical, demographic, molecular, and patient-reported data, as well as data on health resource utilization. Our goal is to create a model for investigating public investment in genomic medicine that maximizes the cost:benefit ratio for the Australian community at large.

Introduction

The genomic revolution is arguably the most significant development in cancer medicine since the microscope. A century of laboratory and clinical research has made it clear that cancer is fundamentally a genetic disease, driven by heritable changes in the cancer genome or chromatin arising either in the germline or during the many subsequent steps required for a normal cell to become malignant. Accordingly, massive technical advances in sequencing technologies witnessed over the past decade have the potential to change completely the way we think about, prevent, diagnose, and treat cancer. The sense of scale involved has driven the development of many large-scale genomic medicine programs, engaging almost every sector of the cancer community: patients, clinicians, clinical trialists, pathologists, clinical geneticists, epidemiologists, health economists, and the biotechnology and pharmaceutical industries.

Personalized medicine

Most of these programs have focused on somatic cancer genetics, and the potential for mapping 'actionable' mutations in patients with advanced cancer (see, for example, Accelerating Progress Against Cancer: ASCO's Blueprint for Transforming Clinical and Translational Cancer Research; http://www.asco.org/practice-research/ascos-research-blueprint). Accordingly, they have tended to include patients with advanced cancer, with the goal of 'precision' or 'personalized' medicine. Here, this concept is taken to mean the use of molecular diagnostics (typically but not exclusively based on tumour DNA sequencing) to select more accurately the right drug for the right patient [1]. The concept from an increasing volume of basic research and clinical trials suggests that the presence of a mutation is predictive of subsequent response to targeted therapies. In some cases, a molecular test has been shown to predict nonresponse and, thus, may avoid the use of futile therapy. This approach, while promising for a subset of cancers (including melanoma, non-small cell lung cancer, and colorectal cancer [2–4]), has yet to be shown to be universally applicable as a clinical approach to cancers more broadly [5]. Overwhelmingly, nascent programs exploring opportunities for genomic medicine have been

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driven from the 'bottom up', so to speak, focused on specific trials, or disease populations, rather than from a public health perspective. The clinical endpoints for such programs are typically progression free or overall survival following exposure to an intervention based on a molecular diagnostic, and typically apply to a small, highly selected group of patients with cancer. The biases relevant to public health are on the spectrum of the cancer population with advanced disease, and are typically skewed to the major conventional subtypes: breast, lung, bowel, and so forth. In most cases, the outputs of population-level molecular testing have correlated with cancer subtype [6–8]. Fascinatingly, it is increasingly clear that 'actionable' mutations do not respect our conventional histologic or organ-specific classifications of cancer. As such, there is a tantalizing suggestion that a molecular classification of cancer might be more relevant to cancer management, although the extent to which this proposition has been tested in clinical practice has been limited.

Research into personalized medicine to date has not sufficiently explored the transformative potential of genomics to impact on cancer subtypes neglected by the current anatomic and histologic classification systems [9]. This is exemplified by the identification of mutations in genes in metabolic pathways in rare cancers, such as paraganglioma, gastrointestinal stromal tumours, and chondrosarcoma [10,11]. These cancers, although individually less common, are collectively a major health issue, and contribute disproportionately to cancer mortality.

The public interest

Public health systems are being challenged to respond systematically to the potential of genomic cancer medicine [5,12]. This is driven in part by the increasing awareness of the public at large of advances in the laboratory and clinical space; partly by clinicians and scientists who believe that genomics will transform healthcare; and partly by commercial interests in the biotechnology and pharmaceutical industries, with whom public health systems have an uneasy but vital relationship. The energy driving public interest derives from the fact that cancer is a major cause of morbidity and mortality in most high and upper-middle income countries (http://www.who.int/healthinfo/global_burden_disease/estimates/en/index2.html). The impact of many 'breakthroughs' in cancer treatment based around molecular diagnostics and cognate therapies has raised expectations regarding the state of readiness of the concept of personalized medicine for routine cancer care [5].

A most striking aspect of the voltage in public debate around personalized medicine is the pressure being brought to bear on public health systems to expedite the implementation of models of care that have not been evaluated in clinical practice outside of clinical trials or high-volume centres. It is arguable that the healthcare system has struggled with the pace of developments and the speed with which new knowledge reaches the public. This is also because of both the inherently conservative nature of clinical medicine and of public healthcare systems in general. Globally, the governments of developed nations are faced with managing rising healthcare costs [12,13]. The costs of public health and medical care, along with aging populations and a proportionally dwindling tax base, are affecting every aspect of public policy, including immigration, taxation structure, regulation of medicine and device approval, and investment in research.

The irony is that the impact of much of the research on personalized cancer medicine might be that, as a society, we cannot afford success, at least as defined by current clinical trials designs and endpoints [13]. It is clear that conventional, patient-centred endpoints need to be complemented by public health and health economic research that explores how the system itself might need to change to accommodate the future of genomic medicine.

Evidence gaps

In this context, the evidence base from which governments make decisions on healthcare investment is surprisingly poor. In Australia, although cancer is a notifiable disease for which we have public registries, the data collected at the population level are limited for the most part to histologic subtype, as well as a minimal demographic data set on each case that includes age, sex, and location. Cancer stage, one of the most important pieces of data relevant to understanding the burden of cancer, is not systematically collected. State-based agencies collect information about activities (attendances, admissions, and procedures) within public hospitals, whereas treatments outside hospitals and provided in outpatient settings in hospitals are independently captured in federal databases, such as the Pharmaceutical Benefits Scheme and the Medical Benefits Schedule. Additionally the healthcare system in Australia is two tier, divided into public and private domains. The private healthcare system, which provides care for perhaps one-third of Australians, is funded by a mixture of out-of-pocket payments, private health insurance, and public subsidy, and represents another silo of information that is not readily captured or integrated with the preceding sources of data.

Crucially, there is little if any systematic collection of patient-reported outcome measures (PROMs) at the population level in any of the repositories described above. Note that this dearth is not unique to Australia [14]. Understanding patients' and the public's preferences for healthcare is crucial for making informed rationing decisions. PROMs that measure health-related quality of life (HRQoL) are pivotal for informed public investment in healthcare; utilization of generic HRQoL measures, rather than disease-specific measures, allows comparisons across the full range of health issues facing a community: the outcomes of neoplasms can be compared with those of cardiovascular disease and musculoskeletal conditions. It is impossible otherwise to decide upon the relative importance to the community of investments in healthcare. Health economists use a generic HRQoL measure (often referred to as a utility value) that is combined with time spent in a health state to produce an estimate of a quality-adjusted life year (QALY). QALYs that reflect both morbidity and mortality can be readily compared across diseases, and used to produce a ratio where the incremental costs of a new approach are compared with the incremental benefits as measured by QALYs. This ratio, referred to as an incremental cost effectiveness ratio (ICER) helps inform decision-making about public health investment in medicines or devices; the cost per QALY gained can be compared across interventions, and provides an insight as to the opportunity cost of investment in personalized medicine, what else (and who else) could benefit from investment elsewhere. It follows that understanding the cost per QALY for cancer care and the uncertainty around the estimate is crucial for effective decision-making by governments. As noted above, existing genomic medicine programs (and cancer trials more generally) focus on metrics such as progression-free survival or overall survival, and perhaps adverse events. The inclusion of PROMs in trials is rare [15], which necessitates extensive modelling to generate the information required to make decisions about the population-level implementation of personalized medicine.

Time is the final dimension that is crucial to any view of public health delivery. Perhaps because of a focus on late-stage disease, most genomic medicine studies have not explored somatic cancer mutations over the cancer journey. The incidence of mutations in KRAS in bowel or lung cancer might differ when considering the initial

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diagnosis compared with subsequent relapse, for example. Moreover, the opportunities for the use of targeted therapies in the early stages of a cancer journey are not known, even for the cancer types in which these mutations have been intensively studied. This is important, because it is likely that targeted medicines will increasingly be tested in earlier stages of disease after initial proofs of principle in advanced settings, as observed with trastuzumab in breast cancer. Certainly, the adjuvant use of targeted therapies would appear to confer the greatest prospects for reducing cancer mortality. Time is also important in a health economic sense. Any decisions about optimum public investment in cancer must consider the possibility that a small overall survival benefit might be offset by more marginal improvements in QALYs during the period of extended survival. In effect, we lack a sense of the area under the QALY curve for each patient with cancer, which will be important for making decisions about investments in high-cost diagnostics and treatments in early versus late interventions.

Cancer 2015: a whole-of-system genomic medicine cohort

In this context, we designed Cancer 2015 as a cohort study that would allow a whole-of-system view of the potential for genomic medicine to impact on cancer at the population level. As described here, this has led to some unique features in study design, aimed at addressing some of the concepts outlined above.

Cancer 2015 has recruited patients with cancer within the state of Victoria from the time of diagnosis, regardless of cancer type or stage. This has allowed us to create a sample corresponding to the burden of cancer in the Victorian community, unbiased by a focus on any individual cancer type (Fig. 1). We have collected from four major treatment centres, including two regional sites, a private cancer centre, as well as a major general hospital cancer unit and a dedicated comprehensive cancer centre. We have collected not only key demographic and clinical data, including cancer stage and comorbidities, but also measures of performance status and PROMs, as well as data on state and federal health costs. An analysis of the determinants of QALYs in the cohort has found that patients with colorectal cancer have significantly fewer QALYs compared with patients with prostate cancer, whereas those with declining performance (as measured by their performance status) have significantly fewer QALYs. The data linkage with state and federal health departments is such that we can access information on resource use before diagnosis as well as during the cancer journey. We find that hospitalization costs are 12 times greater post diagnosis, than pre diagnosis, whereas pharmaceutical costs are six times higher. An analysis of pharmaceutical costs finds that targeted personalized medicines are the most significant driver of cost over time. The site of cancer is also an important predictor of costs for pharmaceuticals, less so for hospitalizations, and not at all for medical services. We have followed each patient over time to capture changes in disease stage and PROMs, along with the nature and cost of healthcare interventions. We are intending to resample patients to compare the genomic profiles of tumour samples at baseline and relapse, including peripheral blood samples for liquid biopsies. We have undertaken a genomic screen using diagnostic formalin-fixed, paraffin-embedded samples, and evaluated the application of these technologies in the clinical setting. Forty-eight common cancer genes were tested in a pilot cohort of 1094 patients using next-generation sequencing. Clinically relevant mutations were identified in 63% of patients, with 26% of patients displaying a mutation with therapeutic implications. Some tumour streams (lung adenocarcinoma, and head and neck squamous cell carcinoma) showed a different spectrum of mutations, which has significant implications for health economic modelling of particular targeted agents. Actionable mutations in tumours not

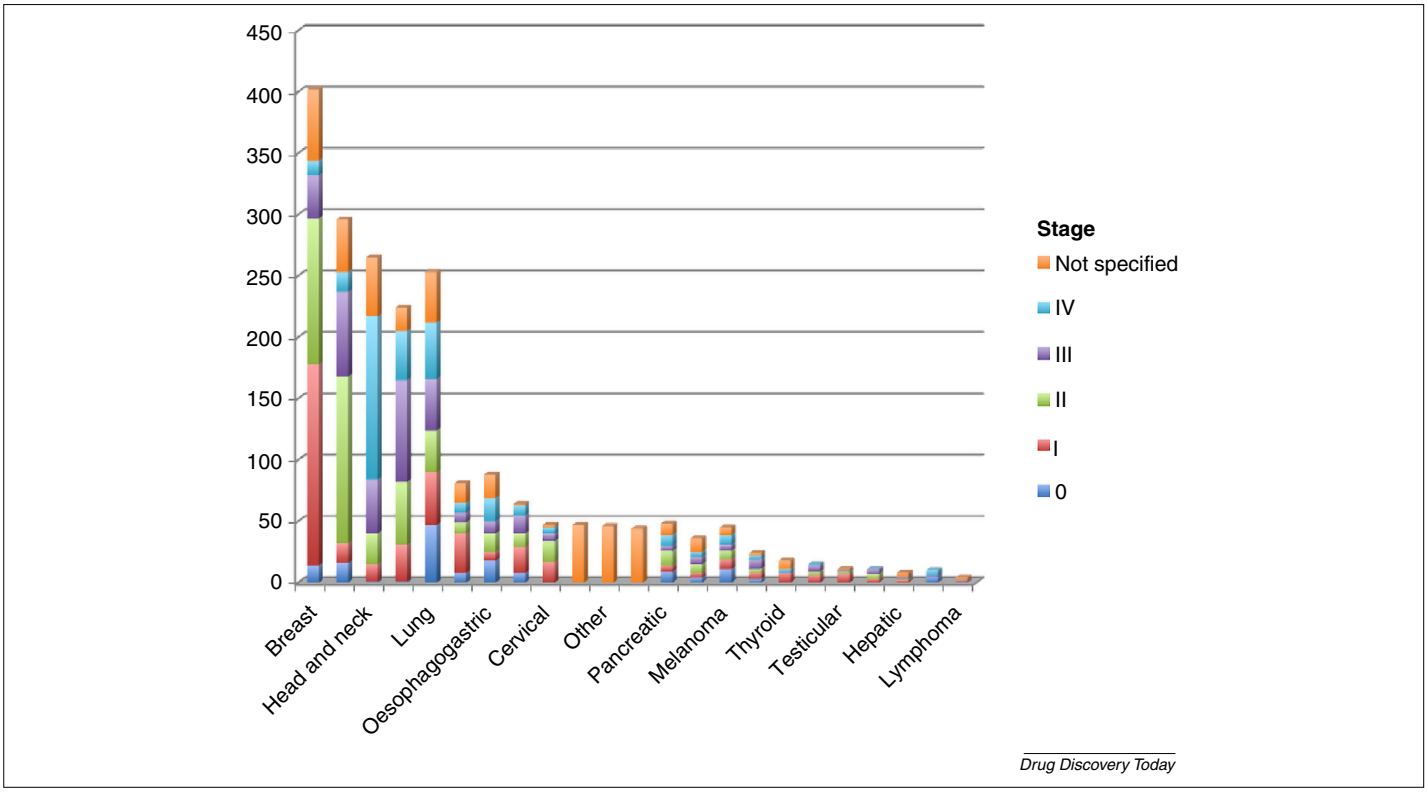

FIGURE 1

Summary of cancer types recruited into the Cancer 2015 cohort, by tumour stage.

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usually thought to harbour such genetic changes were also identified [16].

Concluding remarks

We believe that the data generated by Cancer 2015 will provide the foundations for public health investments in genomic cancer medicine in Australia. By creating a cohort that is large enough to reflect the burden of cancer in the community, we not only contribute detailed insights into current patterns and outcomes for cancer treatment, but also survey potential opportunities for public investment moving forward. This particularly applies to screening cancers that fall outside the hotpots for investment to date, and begins to assay the total potential for application of targeted therapies in the community as a whole. Health economic analyses within this cohort should provide evidence to inform rationing within and rationalization of the healthcare system itself, so as to optimize the social good. This might include modelling the effects of various levers within the Government's control on health outcomes, something that will be vital to public investment in the future. These levers might include greater engagement with the pharmaceutical industry in access to targeted therapy early and at a lower cost; mechanisms to support increased participation in clinical trials and the greater integration of research investment in general in healthcare delivery; broadening the scope of interventions beyond drug trials in advanced disease to consider screening and early detection, prevention, and adjuvant treatments; and addressing issues of equity of access across private, public, regional, and metropolitan service centres. It is an appealing notion that more detailed insights into how cancer is currently treated could be used to model the effect of manipulating the public health system itself in maximizing the benefit from a future that includes genomic medicine. As a collateral benefit, we have set up the fundamental infrastructure for molecular tumour testing at scale, including a baseline for process optimization to meet the demands of clinical practice.

The future plans for the Cancer 2015 program include integration with intervention programs that span the full range of opportunities to improve health outcomes. These include engagement with existing clinical trials, and creation of novel clinical trials that exploit the power of genomics. In addition, we propose to use genomic technologies to better understand differential cancer risk, and link this to new models for risk management. We believe that principles of collecting PROMs and healthcare resource and cost data, and of longitudinal follow-up to determine effectiveness following interventions, will strengthen the evidence base for the much larger systemic investments in cancer care over the next decade.

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