Horizon Scanning Series
The Future of Precision Medicine in Australia

Health Economics

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Introduction

The development of new genetic technologies has the potential to provide significant benefits for health care. For patients, the potential benefits are improved knowledge about the risks of developing disease, the opportunity to mitigate risks through behaviour modification, screening or preventive treatment, and an opportunity to make informed choices (Salari et al, 2012). For health care providers, there may be greater capacity to predict response to treatment and to target treatments more effectively, leading to more certainty and potentially better health outcomes for their patients (Patel, 2014). For industry, new technologies lead to new marketable products and potentially new sources of profits (Marketwatch, 2014). Instead of treating 100 people, with 10% showing a response to treatment, 10 people identified through genomic testing could be treated with 100% response. But all of the 100 people require testing initially and for some of the 90%, other treatments may be indicated. There is an even greater market opportunity if 1,000 people can be convinced to be tested. In some cases, the emergence of the capacity to identify genetic markers has rescued treatments previously thought to be ineffective or harmful, but which may be effective for a targeted population. For the health system, genetic technologies have the potential to lead to more targeted treatment, reducing health care expenditure that is unlikely to lead to benefits, and improving overall efficiency. However, these new genetic technologies can also have significant costs; and many of the benefits remain uncertain (Deverka et al, 2010). The balance of costs and benefits will differ when considered from different perspectives in the health system and for society.

There are likely to be increased costs associated with new treatments and tests (Filipova-Neumann and Hoy, 2014; Gazoulis and Soulitotis, 2014). From the point of view of manufacturers of health care technologies, genetic technologies have the potential for increased revenue from new tests and treatments. But in Australia, as in most developed health care systems, the prices paid for new technologies are generally related to the health outcomes gained, and the capacity to target may lead to higher prices for targeted treatments. This directly impacts on health expenditure through government funded programs, though whether the net effect will be positive or negative or neutral will depend on the balance of new costs and offsetting reductions. Where new technologies are not funded or only partially funded by government, patients will face higher health care costs in terms of insurance premiums or out of pocket costs, often at levels that are beyond the reach of average income earners. This opens questions of equity of access to new technologies. It is also worth noting that the information from genetic testing is rarely certain. As a result, there may also be patients who undergo unnecessary treatment that entails costs and risks but does not provide a benefit. Patients may also experience increased anxiety about potential future health outcomes, and may choose as a result to seek more frequent follow up and treatment even when this does not confer a health benefit (Hall et al, 1998) . There is also potential increased anxiety if the ability to identify a risk of has outpaced the development of treatment options for that condition.

This chapter examines the implications of these new technologies for the health care system. However, an answer to the value of precision medicine depends on how health care is funded, how

value for the health dollar is determined, and how the health technology market is regulated (OECD, 2011). Australia is a mixed public and private health care system. This raises the question about what should be covered under universal health insurance ie Medicare, and what should be left to private funding. Australia has a well developed health technology assessment approach but evaluating genetic tests and genomically guided treatments presents new challenges. The rapid development of this technology is leading to lower up front testing costs, although these may result in increased use of high cost interventions and this presents challenges for market regulation. Further, the availability of low cost testing may result in increased demand for treatments that may not yet have demonstrated benefits, or for which the capacity for harm remains as yet unknown.

Public and private payer systems.

The financing of health care in Australian is primarily by government, accounting for around two-thirds of health care expenditure. The other main sources of finance are private health insurance and out-of-pocket (OOP) expenditure. Funds are then expended through both public and private sectors. Medicare provides subsidies for treatment provided by private medical practitioners, including diagnostic testing. Private health insurance covers private in-hospital treatment and/or general (largely dental and other ancillary services) and is prohibited from covering out-of-hospital services provided under Medicare. Over the last decade, there have been a series of initiatives using both subsidies and penalties to encourage the uptake of private insurance; currently slightly less than half the population have private insurance at a cost of $6.5b in public funding. Consequently, significant public funds have been directed to support the private health insurance industry and, by extension the private health care sector.

The result of these complex arrangements means that any particular episode of care may be funded through different mechanisms and from different sources. The use of precision medicine will generally involve initial testing to determine the genetic makeup of the patient and, in the case of cancer where much of the development of genomic medicine has occurred, that of the tumour. The results of that test may provide information that will allow the clinician to recommend the most appropriate therapy, particularly where there is a targeted treatment available, or where there is information about potential harms of some therapies.

Consider a diagnostic test for a genomically related cancer that has a genomic marker with a potential targeted medicine. The test may or may not be covered by the Medicare Benefits Schedule, but will likely include a consultation with a specialist, a biopsy, as well as pathology, and will likely involve a private provider. The extent to which patients have to pay out of their own pocket in the community setting will depend on the fees charged by their provider and the Medicare Schedule Fee. In addition, the Extended Medicare Safety Net (EMSN) (introduced in 2004) provides some additional financial protection for those patients who incur very high out-of-pocket costs (and higher costs for government) during a calendar year relating to Medicare services delivered in the out-of-hospital sector.

However, many different types of genomic tests are not listed on the MBS. Through their public hospital linked facilities, state governments have established and funded many genetic services that will offer genetic screening, as well as counselling and education services. Such services are limited in their physical location, with different funding arrangements across states and territories, and typically cater to individuals who have been identified as being at risk of a genetic condition. Any

consequent treatment may be provided through a public hospital at no charge, or if the patient has private insurance they may elect to be treated privately in a public hospital or in a private hospital. Each of these alternatives involves different costs for the patient, the private insurer, the State and Commonwealth Governments. Subsidies may also distort the distribution of government benefits.

Insurance

Medicare provides universal tax financed comprehensive insurance but it does not cover all health care services, and this is particularly the case for emerging technologies which have not yet undergone health technology assessment. The process by which new technologies are assessed for public subsidy is discussed in the next section. In the context of precision medicine it is important to note that Medicare has been intended to provide 'medically necessary services' and this has not included population based screening. Major population screening programs such as cervical cancer, breast cancer and colon cancer have been funded as separate population health programs. There are some advantages to this approach as national screening programs can be designed to encompass appropriate counselling, education and follow up, and to provide a more efficient approach to recruitment, delivery and targeting of services. However, once a condition is detected, further investigation and treatment is deemed medically necessary and covered by Medicare.

The question arises about what genetic information testing and treatment technologies should be publicly funded. For an individual pathology test for a particular genetic marker (for example a hereditary disease) this is managed through the evidence based reimbursement decision-making process (MSAC). But genomic sequencing (as opposed to genetic testing related to specific risks) is unlikely to be assessed through this process, and yet it could become a de facto approach to screening for particular risks or diseases. If such an approach to screening becomes widespread, even though not funded under Medicare, there will be inevitable consequent costs on Medicare for further follow up and treatment unless the fundamentals of Medicare are changed. There is also the evidence that changing information can change peoples' behaviours including seeking more health care and potentially increasing total costs (MacDonald et al, 1984).

Private insurers may choose to cover such genomic sequencing, subsequent testing and follow up, through their 'general' or ancillary products. Private insurers are allowed to operate 'health businesses' and have recently established or acquired interests in the provision of dental and optical centres and primary care. Where genomic testing has clear benefits, and the tests are not yet covered by Medicare, this could be a significant challenge to the equity of the Australian health care system. Even when the benefits are not clearly demonstrated, this introduces differential access. The other aspect of equity is how taxation revenues are redistributed to the benefit of the population.

The issues for further consideration are

- Where should the responsibility for funding of genomic technologies fall, particularly in a mixed public private health system such as Australia's?
- Which genomic technologies should be funded or subsidised publicly and what are the implications of access through the private system, in terms of equity and efficiency?

Assessment of risk factors

Genomic testing will provide much more precise information about individual risk factors and this may be generated by family members choosing to be tested; results have implications for related individuals even if they choose not to be tested. Risk assessment may be altered in private health insurance, in other insurance, and in occupation selection.

Although private health insurance in Australia is community rated (so individual risk should not affect the premium charged), firms do attempt to encourage better risks to take out insurance; for example, policies that are targeted at young people. Testing will provide new approaches to favourable risk selection and while this will improve private firms' profitability, it runs counter to the social goals of community rating for private health insurance. On the other hand, should firms be obliged to provide cover to individuals with known conditions where the probability of an insurance payout becomes higher, or to provide packages that cover all conditions? There are questions to be asked about individual responsibility to disclose risk; and equally at what point they should seek treatment.

The same issues arise in the context of other insurance, particularly life insurance and income cover, though we may also include travel insurance. These markets are less highly regulated.

Finally more precise information will provide some insights into the riskiness of certain occupations. This may benefit the individual in selecting an occupation but would also be valuable to employers in recruiting staff. It is feasible than just as psychological testing for job attributes has become widespread, that employers could seek genomic testing as basis of candidate selection. This has implications for regulation in terms of the mandating of pooling of risks, and the level at which this risk pooling should occur for the population.

The issues for further consideration are

- What are the implications of genomic technologies, including genetic testing and precision medicine for private health insurance in Australia?
- Should individuals be required to disclose their testing history to insurers, to employers, or others?
- Should insurers, employers or others be prohibited from seeking information about testing history from individuals?
- What are the implications for other insurance markets including life, income and travel insurance?
- Should employers be able to require genetic testing?

Cost effectiveness and Resource Allocation

The previous section identified how in Australia's mixed public-private system the developments of precision medicine can lead to changes in the costs of health care, and the distribution of those costs across governments, and individuals. The way that these new technologies are financed and funded has an enormous bearing on the efficiency, equity and sustainability of the system. It is also

important to recognise that the funding mechanism will have consequences; for example, fee for service will generally result in larger volumes of services. New technologies generally have high overhead costs associated with the process of discovery and bringing them to market. A funding mechanism must recompense these fairly and provide incentives for additional advancement while not allowing providers to capture abnormally high profits.

Costs of implementation

The costs of implementation can be considered in two categories, the cost of providing the service based on the technology itself and the need for associated infrastructure.

The cost of any service delivery is a combination of fixed and variable costs. The relationship between the two determines whether there are economies of scale. In many health care services there are volume-outcome relationships, whereby a minimum level of activity is required to ensure good quality outcomes. Investigation of economies of scale, economies of scope and volume outcome relationships is required to ensure technical efficiency in the delivery of these services.

It is important to understand that testing in itself does not deliver improved health outcomes, rather it provides information which can be used as a basis for further intervention (Rubin et al, 2014; Cairns and Shackley 1993). The information changes the consequences in terms of health care use and costs. Overall, the net costs may be negative or positive (but should be weighed against health gains as discussed in the next sub-section). It is well established that fee for service is associated with increased volumes and that some of those services will be less effective or even wasteful. Health reform is seeking new approaches to funding which provide more appropriate incentives for practice. Where a service is part of an episode of care, bundling those services may well be a more effective funding mechanism. Another consideration is funding mechanisms that will enhance high quality care. In the context of genomic medicine, such funding mechanisms might ensure that services are better targeted to those who stand to benefit, and that the use of the resulting information results in the appropriate downstream use of health care. The development and implementation of such innovative funding approaches has not proven easy so far, but will have significant effects on the cost of delivery.

There will also be an associated infrastructure required around the storage of genetic material and the confidentiality of data (McGowan et al, 2014). Storage of information and the capacity to re-test is important because there may be changes in the interpretation of results as more information from research becomes available – there may be re-testing of new markers, or changes in management based on new information about the existing and known markers. Health information is known to be particularly valuable on the dark web and there are increasing risks to cybersecurity. There are also medico-legal and ethical implications around the responsibility to act on information; for example, if a test identifies a familial risk of a potentially severe condition, should family members be informed even though they have chosen not to be tested?

The issues for further consideration are

- Are there delivery systems implications (e.g. economies of scale, volume-outcome relationships) for genomic testing and treatment?

- What are the appropriate funding mechanisms to ensure efficient provision of appropriate and high quality services?
- Who is responsible for the provision of infrastructure associated with genomic technologies (including storage of genetic information and genetic samples)?
- What are the ethical and legal responsibilities for provision of information to other parties?

Ensuring value for money

Australia has a well-developed process for assessing new medical technologies for public subsidy. The need for a rational process and one that is consistent across funding programs in deciding on whether to fund a new technology is driven by the limited resources available to pay for health care. Australia has introduced formal structures to assess the cost-effectiveness of new technologies and these are part of both the Pharmaceutical and Medicare Benefits Schemes, and are in addition to the regulatory structures that are in place to consider the safety and efficacy of new technologies.

There have been a number of reviews of economic evaluation studies in precision medicine (see for example Antonanzas et al, 2012; Assasi et al, 2012; Buchanan et al, 2013; Beaulieu et al, 2010; 2013; Djalalov et al, 2011; Jarrett and Mugford, 2006; Marzuillo et al, 2014; Miller et al, 2014; Phillips et al, 2014; Simonds et al, 2013; Vegter et al, 2008; Wong et al, 2010; Yang et al, 2013). As precision medicine can vary in its focus, from screening to targeted therapy, and across diseases, it is difficult to reach general conclusions about the cost-effectiveness of the technology. There are inconsistencies in the approach taken in individual studies, and in the ratings of quality by reviewers. For example, in an extensive review of cost-effectiveness analyses for CRC, Frank and Mittendorf (2013) observed significant variability across studies, concluding that the key drivers of the results were: how the costs for the detection of predictive biomarkers were included (not at all, only for patients who receive the targeted agent, for all patients); the clinical characteristics of predictive biomarkers (sensitivity, specificity, validity, reliability, timing, prognostic value, testing sequence and incidence); and the data for the targeted agent (based on retrospective subgroup analyses, incorporating heterogeneity of effects, or individualised dosing). However, some general findings about the challenges for economic evaluation emerge.

While genetic technologies are just another category of new health care technology, and so should be assessed within the same broad framework of health technology assessment, there are particular issues that arise in consideration of their cost-effectiveness (Deverka et al, 2010; Grosse et al, 2018). It is important to identify how genomic technologies, and particularly different sorts of technologies (eg genomic sequencing, tests for specific genes or tests for tumour markers) change the treatment algorithm at different points, and what the implications are for treatment. The choice of comparative technology against which costs and outcomes are assessed is another issue (Buchanan et al, 2013). The choice of comparator for genomically guided cancer care should ideally involve a mix of genomic and non-genomically guided care. Multiple comparators may also be of value, particularly when applied to diagnostic tests where there is a potential for the use of in-house custom tests of differing cost and analytical validity.

The choice of perspective is key to identifying the scope of outcomes and costs included in the analysis. Choosing a narrow perspective – such as a health care perspective – can potentially overlook many of the potential benefits and costs of genomically based technologies. An example of this is the value that consumers may place on information provided by genetic tests that potentially

go unmeasured or unvalued when the study's perspective is restricted to a health system perspective. Similarly, information may have a negative value if it increases anxiety or concern.

Economic studies of genomically guided cancer care also require appropriate timeframes to ensure that all downstream costs and benefits are captured. Importantly, economic evaluations of many genomically guided cancer care technologies are an amalgam of two different technologies: the test and the treatment. This inevitably makes the evaluation more complex and generates more uncertainty around some of the key parameters of the study such as the sensitivity and specificity of the test results. This makes it important to undertake well-specified sensitivity analyses that can provide information on the importance of such uncertainty on the overall results.

Current health technology assessment approaches rely on clinical evidence produced by clinical trials. Robust trials require a large group of homogenous patients (for statistical significance). In contrast, precision medicine is exploiting the differences across individuals to better target therapy. This produces a particular challenge in generating scientifically valid evidence, one that is shared with rare diseases (Rare cancers Australia 2017). Adding to this complexity, scientific knowledge is expanding at a rapid rate and is likely to change the relationship between genetics, disease progression and therapy. This complex relationship suggests that it is difficult to assess (or predict) what the overall impact of genomics is on the health care system in terms of health outcomes, costs and delivery.

The decision making processes for listing pharmaceuticals were designed in an era when blockbuster drugs, prescribed to large groups of patients, were commonplace. The additional costs that HTA processes imposed on pharmaceutical companies and governments (such as the costs of producing a health-technology report, conducting economic evaluations and undertaking rigorous assessments) were relatively small compared to the overall revenue that could be gained by listing a drug on the PBS. However, the blockbuster era has gone and the current pharmaceutical market is characterised by more therapeutics for multiple indications and smaller patient groups. This trend is likely to continue with expansion of genomically-guided treatments; where the patient population is getting smaller and the volume of sales for each new therapy is decreasing.

Therapeutics with smaller potential markets may increase the relative costs of undertaking HTA compared to potential volume of sales. Given that the costs of conducting an HTA is fairly fixed (i.e. the costs are unlikely to vary much regardless of the sales volume) its expense may start to put additional pressure on drug prices. These issues may come to the fore with the development of personalised medicine. Under circumstances when the target population is so small, our current HTA and decision making processes may become too cumbersome, and alternative priority setting mechanisms for deciding which technologies to adopt and diffuse may need to be designed.

The issues for further consideration are

- Are the current structures for assessing new technologies (e.g. MSAC, PBAC) appropriate for assessing new genomic testing and treatment?

Regulation of private markets

There are large potential benefits offered by precision medicine, and the potential for increased cost pressures on health care budgets. With the rapid development of technology leading to lower costs for genetic sequencing, and the potential for new market driven opportunities, it is important to ensure appropriate regulations (and incentives) exist to ensure cost-effective use of these new technologies. The policy response will have to address better targeting of genetic tests to particular population groups, as well as influencing and informing patients and clinicians about appropriate surveillance activities, and ensuring that post market surveillance is part of the infrastructure.

Health care is seen as a growth industry by investors in the Australian economy as Australians are prepared to commit more discretionary spending to health, the population is ageing, and most health care services are underwritten by government. This provides a context in which private profit can conflict with social objectives.

Pop-up clinics and diagnostic services

New technologies often provide a niche market for new providers to specialise and develop new customers. This is particularly so when consumers can be recruited directly, that is without referrals from GPs. A screening test can be useful as a marketing tool and may be offered as a loss leader, particularly if covered by Medicare and so can bulk billed. Positive test results can then be recalled for further investigation or treatment. Of course, this provides an incentive to err on the side of classifying more tests as positive, and to recoup costs on further tests/treatments.

The development of skin cancer clinics is a case in point. These have proliferated, and have been accompanied by increases in skin cancer treatment MBS items charged. Although such services appear specialised, they are generally staffed by generalist trained doctors rather than dermatologists.

The issues that arise for consideration are

- How should the provision of clinics and diagnostic services be regulated to ensure appropriate use of these technologies and safeguard patient interests?

DIY kits

There has been rapid growth in this part of the market, which can be characterised as using direct to consumer advertising, taking DNA samples at home, and submitting those to a testing laboratory. The growth of internet sales and international commerce has facilitated this market. It also makes it difficult to regulate providers if they are based in another country. The potentially adverse consequences of this form of testing include poor standards of non-accredited providers, little relevant information, lack of follow up and counselling services, lack of connection to other health care providers, consequent anxiety for consumers, and increased demand on in-country health services (to deal with the results of such testing, regardless of its accuracy).

The issues that arise for consideration are

- Can Direct to Consumer advertising be regulated?
- Can the use of these services be managed to ensure appropriate use of these technologies and safeguard patient interests?

- Can quality of laboratories providing genomic profiling be regulated, especially if they are based outside Australia?

Pharmaceutical Industry

The pharmaceutical industry has the potential to benefit from the development of targeted treatments, which may command substantially higher prices. Currently, the highest returns are made from products for which there are large segments of the population and products which will only benefit a small number of patients are less commercially attractive. The industry also bears most of the costs of drug development (noting that much basic science is still supported in universities) and these have to be recouped whether the product is for a common or rare disease. To date, the Australian government has recognised the need to provide different arrangements for the funding of treatments for rare conditions, including rare genetic conditions, through the Life Saving Drugs Program. The challenge is to encourage more therapies that can be directed towards smaller patient groups within the general Pharmaceutical Benefits Scheme. It is of note that the prices paid by government are often related to therapeutic benefit for a particular patient group; consequently the same drug could attract different funding in different patient groups.

The use of economic evidence in determining public funding is a powerful tool for policy makers for increasing value for health care expenditure, but decisions are more uncertain where economic evidence is lacking. Clinical and economic evidence takes time to develop, and meanwhile patients may be denied beneficial treatments. One response to this challenge is to provide coverage with evidence development, such as through risk-sharing arrangements, with the condition that more evidence is collected with the supplier at risk for a product which proves to be less effective. Thus far, risk-sharing arrangements have taken on many forms:

- Agreements that are designed to limit uncertainty regarding costs without taking into account the health outcome experienced by the patient. For example, the manufacturer paying for the genetic test in order for patients to gain access to a drug that is subsidised on the PBS for individuals with tumours that exhibit specific mutations.

- Price volume arrangements that restrict the financial liability of the payer by placing a cap on their total expenditure. These agreements allow the payer to be reimbursed if the total expenditure exceeds the cap.

- Performance-linked reimbursement arrangements designed to limit uncertainty regarding the cost-effectiveness of a new drug in the real world. For example, under the funding of ipilimumab for melanoma, the funder only pays for the treatment for those patients that respond.

- Coverage with Evidence Development (CED) arrangements that link population-level payment or reimbursement to prospective data collection.

Despite the obvious attraction, risk sharing agreements have frequently been difficult to implement (Neumann et al, 2011). Some risk-sharing arrangements require substantial new capacity to monitor costs and outcomes of new therapies in real world settings, particularly those that are based on performance-linked reimbursement arrangements that require patient-level outcome measurement. This capacity is often lacking, or requires substantial investment.

Thus far, risk-sharing agreements have typically been established between the payer and the pharmaceutical manufacturer. However, Ramsey and Sullivan (2014) propose that in the case of genomically guided care, risk-sharing agreements between payers and cancer care institutions are worth considering. One of the main reasons for this proposition is that treatment outcomes are not just predicated on the effectiveness of a drug, but also on the accuracy of the genomic tests as well as clinical decisions of who and how to treat. Hence, under traditional risk-sharing agreements between payers and manufacturers, the drug company stands to make losses on the basis of decisions that are possibly not in its control. Realigning the agreement between payers and cancer care facilities could address this issue. Under such an agreement the facility receives greater flexibility to offer patients new therapeutic treatment, but bears the financial costs of these decisions if certain pre-determined clinical benchmarks are not met. This creates strong incentives within facilities to ensure that the most accurate genetic tests are offered and that treatments are matched to patients most likely to benefit. Despite these potential advantages, such risk agreements would still require a sophisticated data infrastructure to enable outcome measurement, as well as measures to protect facilities from excessive risks.

The issues for consideration are:

- How do we ensure that the financial gains associated with the benefits of genetically guided treatment are appropriately shared between the developer of the technology and the taxpayer.
- How do we design payment arrangements for genetically guided treatment to ensure a fair sharing of risks between the developer of the technology and the taxpayer.
- How can we build on existing data collection systems to facilitate monitoring for new risk sharing arrangements?

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