Horizon Scanning Series
The Future of Precision Medicine in Australia

Social and Ethical Implications of Precision Medicine

This input paper was prepared by Dr Wendy Lipworth and Professor Ian Kerridge (Sydney Health Ethics University of Sydney), and includes material on regulation drawn from the input paper prepared by Professor Dianne Nicol and Professor Margaret Otlowski (Centre for Law and Genetics, Faculty of Law, University of Tasmania)

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Social & Ethical Implications

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1. Introduction: thinking "ethically" about precision medicine

Precision medicine has significant potential to improve the lives of both individuals and populations, but targeted therapies can be expensive, have serious adverse effects and are not always as effective as hoped. It is crucial, therefore, that the "right" targeted therapies are developed, and that these are tested, regulated, funded and used in practice in the "right" ways. It is not always easy, however, to determine what is right because precision medicine affects, and is shaped by, many different stakeholder groups—including patients, clinicians, government and industry—each of which has its own, often strongly held and competing, concerns and commitments. These, in turn, determine what they consider to be good and right.

In each case, these perspectives are underpinned by values such as autonomy (which in this context usually refers to self-determination), beneficence (doing good), non-maleficence (not causing harm), justice, solidarity, and integrity. People also value the pursuit of knowledge and the social benefits that derive from scientific inquiry. In this chapter, the ethical issues raised by precision medicine are summarised with reference to such values and ideas. The aim is not to fully articulate stakeholders' perspectives or to provide answers to ethical dilemmas, but rather to map the moral territory of precision medicine. This chapter focuses on the ethics of the development, regulation and funding, and clinical use of "targeted therapies" developed using genomic technologies.

2. The ethics of developing and testing targeted therapies

2.1. Identification of therapeutic targets

There are numerous ways in which potential molecular targets for precision medicines can be identified, each of which raises its own set of ethical issues. When cell, animal or embryonic models are used to identify genes and proteins that contribute to disease, the ethical issues that arise are similar to those raised by any kind of laboratory research (such as animal welfare, the moral status of embryonic material, and research integrity). More commonly, however, potential targets for precision medicine are identified by finding patterns in the DNA, RNA or proteins of diseased and normal human cells that may provide information about the aetiology, expression, prevention and treatment of disease.

For this kind of "molecular epidemiology" to work, many hundreds or thousands of tissue samples are required. The collections of such samples are most commonly referred to as biobanks. While these samples can theoretically be completely anonymised, analysis is most productive if samples are linked to data about the donors' exposure to risk factors, disease progression and treatment responsiveness. For the purposes of this chapter, collections of tissue and linked data are referred to as "databanks", and the research that they facilitate will be referred to as "databank research".

2.1.1. The ethics of databank research

The collection, storage and use of human tissue and data for research purposes raises numerous ethical issues. Key among these are how to obtain consent for storage and use in unspecified future research; maintenance of donors' confidentiality; interpretation and management of incidental findings; ownership and control of tissues; acknowledgement and management of cultural sensitivities; reporting of results; community participation; benefit sharing; return of materials to communities; and disposal of unused material (Lipworth 2004; Lipworth, Ankeny and Kerridge 2006; Lipworth, Forsyth and Kerridge 2011; Morrell et al 2011). The need to link tissue and data from different sources creates further ethical and regulatory challenges, particularly related to consent, privacy, custodianship and data sharing.

Relevant laws and guidelines:
At present, there is no legislation in Australia that explicitly deals with databanks, and therefore databanks most commonly have their own policies and procedures. These databanks do, however, have to comply with Australian laws regarding, for example, consent, privacy and human tissue, or they risk prosecution. In addition, the National Health & Medical Research Council's *National Statement on Ethical Conduct in Human Research* (henceforth *National Statement*) and the *Australian Code for the Responsible Conduct of Research* provide important ethical and legal guidance for Human Research Ethics Committees (HRECs) overseeing databank research.

Confidentiality and privacy

While participants in databank research are subjected to only minor physical risks (such as those associated with blood collection), they also face the risk of their data, including that derived from tissue samples, being accessed by unauthorised parties. In this regard, it is noteworthy that insurance companies are allowed to demand that applicants disclose genetic results derived from research studies, notwithstanding that such results are typically not generated in accredited testing laboratories.

As databanks become larger and more extensively linked, there is a both a greater need to protect confidentiality and greater challenges associated with doing so. This is partly for practical reasons and partly because of a blurring of distinctions such as those between health-related data and non-health-related data, between personal and non-personal data, between identifiable and anonymous data, between individual and group-level privacy, and between 'primary' and 'secondary' uses of data. These distinctions often form the basis of policies and regulation regarding confidentiality (Lipworth et al 2017).

It is important to bear in mind that informational norms are shifting and many people now freely share highly personal data that can be used for research—for example through social media platforms. At the same time, privacy advocates are fighting for more stringent data protections. It thus remains to be seen what the norms for data sharing and secondary uses of personal data will be in years to come (Lipworth et al 2017; Schadt 2012).

Relevant laws and guidelines:
As a form of 'sensitive information' health information is given enhanced protection under the *Privacy Act*, as is genetic information that is not otherwise health information. This translates into specific requirements for research practices, which the NHMRC *National Statement* outlines. According to the *National Statement*, it is up to individual databanks to justify whether to make samples or data "identifiable", "re-identifiable" (coded) or "non-identifiable". The Statement is, however, explicit that "with advances in genetic knowledge and data linkage, and the proliferation of tissue banks of identified material, human tissue samples should always be regarded as, in principle, re-identifiable".

Consent

Obtaining consent from research participants is one of the key ways in which biomedical researchers demonstrate respect for research participants' autonomy. However, obtaining informed consent for databank research is complicated by:

1. the challenges of obtaining consent from large numbers of research participants across a large number of institutions;
2. the fact that tissue and data are often collected for unspecified future research purposes, making it necessary to consider whether consent can be open ended or whether participants need to have more control; and
3. the fact that tissue and data used in research are often collected for non-research (clinical or administrative) or even non-medical (for example social media) purposes using a wide variety of more or less consistent and adequate consent mechanisms (Axler et al 2008; Lipworth, Ankeny and Kerridge 2006; Lipworth et al 2009).

It is now broadly accepted that for tissue and data to be used in research, consent from participants is required. Models of consent that are generally deemed acceptable are:

1. project-specific consent, in which participants are approached each time their tissue or data is used;
2. categorical consent, in which individuals specify which uses of their specimens and data are acceptable and which are not (people might, for example, consent to only certain types of research, to research in particular settings or to research conducted by particular researchers); and
3. open-ended consent, in which participants allow researchers—under the guidance of ethics committees—to determine how tissues and data might be used.

Relevant laws and guidelines:
Australian Privacy legislation at both the Commonwealth and state levels requires biobanks to ensure privacy in the collection, storage, use, access to, and release of personal information. Since health data and genetic information is "sensitive personal information" according to the *Privacy Act*, it may only be collected with consent, except in specified circumstances. The *Human Tissue Act 1983* (NSW) and associated Directive state that tissue can only be collected after donors have given written, revocable consent. This consent does not need to be project-specific.

The NHMRC *National Statement* asserts that consent to databanking should be in writing, voluntary, and given after participants have been provided with explicit information and opportunities for further explanation. In addition to being informed about the research, potential participants need to be told about their right to withdraw (including any limitations on this right), the potential for commercial application and distribution of benefits, and conflict of interests of anyone engaged in collecting, processing, storing or distributing research materials.

The Statement requires human research ethics committees (HRECs) to approve the consent procedures to be used before samples can be collected. The Statement also requires participants to be informed if any changes are made to the use of their tissue or data after consent has been obtained. Research participants should be free to withdraw without needing to give any reasons for their decisions.

With respect to the various "levels" of consent, the Statement says that consent may be "specific", "extended" (to closely related projects or projects in the same general area of research) or "unspecified" (given for the use of data or tissue in any future research). The Statement is explicitly supportive of open-ended consent, provided there is clarity about the justification for such consent, and about any restrictions that apply.

While consent is a central legal and moral principle, public opinion seems to support the view that respect for autonomy is not absolute, and that the potential contribution to public wellbeing of scientific research may be sufficiently great to allow consent not to be sought if specific criteria are fulfilled (Lipworth, Forsyth and Kerridge 2011).

Relevant laws and guidelines:
Guidelines on exceptions to consent requirement are found in sections 95 and 95A of the *Privacy Act*. The Guidelines stress that a person's right to privacy can be waived when the public interest in research activities substantially outweighs the public interest in the protection of privacy. This may, for example, be because databanks already exist for which no consent has been obtained, or because obtaining consent prospectively would be too onerous.

HRECs are responsible for determining, on a case-by-case basis, whether such waivers should apply. While HRECs are not bound by previous decisions, some consistency is encouraged by the NHMRC *National Statement*, which provides clear criteria for "opt out" processes and waiver of consent. Factors that need to be taken into consideration include:

- The risk to participants;
- The potential benefits of the research;

- The existence of mechanisms to protect research participants' privacy and the confidentiality of data;
- The likely significance of consent bias if consent requirements are imposed;
- The existence of a plan for returning clinically significant results; and
- The existence of clear governance processes and consistency with State, federal, or international law.

When researchers want to allow participants to opt-out of participation in research, they need to show that they will provide adequate information about the opt out process, and adequate time for participants to decline. When researchers wish to seek a complete waiver of consent, they need to demonstrate that it is likely that participants would have consented if asked, show that commercial exploitation is unlikely, and have a plan for making research information available to participants.

Questions about consent become more ethically complicated when the tissue or data that is being used for research is collected in the course of clinical care and stored in, for example, pathology laboratories, electronic health records or administrative databases. The data generated in this way is often referred to as "real world data" and the use of such data in research is seen to be at the core of so-called "learning healthcare systems" in which clinical, administrative and research activities are intimately intertwined (Lewis, Lipworth and Kerridge 2017). While there is no *a priori* reason that consent requirements should be any different in this context, it is increasingly recognised that the need to obtain explicit patient consent for the use in research of routinely collected clinical or administrative data can be resource intensive and lead to biases as a result of differences between consenters and non-consenters, such as those related to gender, socioeconomic status, or health status. The question of whether, when and how consent should be obtained for secondary research use of clinical and administrative data is still unresolved (Ioannidis 2013; Kaplan 2016).

Relevant laws and guidelines:
The NHMRC *National Statement* notes that, where human biospecimens have been obtained for clinical purposes and have since been retained by an accredited clinical pathology service, the biospecimens may be used for research purposes if they been anonymised, or, if identifiable, a waiver of consent has been obtained by the researchers wishing to use the sample.

A common theme in discussions of consent to databank research is that there is an urgent need for new models of consent such as 'dynamic consent'—a form of project-specific consent that makes use of web-based platforms (Kaye et al 2015) , 'meta consent'—where people specify what kind of consent they would like to give for particular kinds of future research (Ploug and Holm 2015) and 'portable legal consent'—where people 'donate' data for research after signing a standardised consent form, and users sign a contract regarding compliance with particular data use provisions (Schadt 2012). Alternative methods of governance, such as participatory governance, in which tissue and data donors are direct participants in research governance and engage in collective decision-making, are also being explored (Dove, Joly and Knoppers 2012; O'Doherty et al 2011).

Incidental Findings

Databank research can produce incidental findings that are not directly related to the research question being asked but that may have clinical significance. Because research laboratories are not subject to the same quality control as are clinical laboratories, the quality and clinical significance of these findings can be uncertain.

Relevant laws and guidelines:
Privacy laws give individuals the right to know what information is being held about them. In the context of genomics, in particular, the right not to know is also increasingly recognised to be

important. There is not as yet any resolution to the question of whether this "right not to know" can or should be enshrined in law.

The NHMRC *National Statement* says that information about return of results and incidental findings needs to be part of consent. In recognition of the moral and scientific complexity of deciding whether or not results should be returned, the *National Statement* does not demand that criteria be fully specified in advance, but rather that researchers should have an "ethically defensible plan" in place. The Statement declares that: "whenever research using re-identifiable data reveals information that bears on the wellbeing of participants, researchers have an obligation to consider how to make that information available to the participants".

Data Sharing, Control and Custodianship

Because databank research involves the long-term storage of data and tissue, these resources can be used repeatedly, and decisions need to be made about who should be able to access the data and material, and, for what purposes. While it might be ideal, in terms of autonomy, for research participants to make these decisions on a case-by-case basis, this would require detailed project-specific consent which is not always feasible or desirable for the reasons described previously. This brings to the fore the importance of appropriate governance of databanks, including appropriate custodianship of tissue and data (Lipworth et al 2017).

Relevant laws and guidelines:

The NHMRC *National Statement* does not discourage data sharing, but does note that:

"some uses of data in a databank may be detrimental to people to whom the data relate. Researchers and/or custodians should consider denying or restricting access to some or all of the data for those uses."

There have recently been several inquiries and public consultations in Australia on "big data", which suggest that Australia is moving towards a system that is more supportive of data linkage and sharing. For example, a *Senate Select Committee on Health* recently recommended streamlining data linkage across Commonwealth and state health datasets; reviewing privacy regulation and legislation to improve access to de-identified MBS, PBS and other Commonwealth data, and normalising data sharing and open access to de-identified data (Parliament of Australia 2016). A Productivity Commission Inquiry recommended "fundamental and systematic changes…to the way Australian governments, business and individuals handle data" including a new Data Sharing and Release Act; a new National Data Custodian; a suite of sectoral Accredited Release Authorities; broad access to National Interest Datasets (NIDs) and (of particular relevance to health-related data) new arrangements for higher risk data to be shared with trusted users (Australian Government 2016).

Commercialisation and Benefit Sharing

In part because it is so expensive, databank research is a 'mixed economy', funded and controlled by both public and private entities. While privately funded databanks are not necessarily any less ethically robust than are publicly funded banks, private control and funding inevitably change the nature of relationships between data donors and custodians (moving away from fiduciary relationships based on trust and professionalism and towards commercial models). Commercialisation also makes it less likely that tissue donors and their communities will benefit from the products of the research (Lipworth et al 2017).

Relevant laws and guidelines:

Australians currently do not have property rights in their own tissue, but tissue becomes property when work and skill is applied to it. The legal argument has been made that this misconstrues the research relationship, which is not a therapeutic (consent-based) relationship but rather a gifting relationship. In this context, consent is an insufficient means of managing the relationship because it fails to take into consideration the realities of, for example, benefit sharing and intellectual property (Stewart et al 2014).

2.1.2. Networking and globalisation of databanks

All of the ethical issues discussed above become more complex as databanks become more networked—including across national and international borders. The networking of databanks increases their statistical power, facilitates the sharing of resources and expertise, and minimises duplicate investment, but also creates numerous ethical challenges. For example, globalisation and networking make it more difficult to obtain consistent consent from research participants and to ensure that confidentiality is maintained. Globalisation and networking of databanks also challenge community values including trust, custodianship, benefit sharing, equity, respect for cultural difference and individual or community control over the use of their tissue and information—values that may be particularly salient to Indigenous communities (Hoeyer 2012; Lipworth et al 2017; Mason, Lipworth and Kerridge 2016a; Mason, Lipworth and Kerridge 2016b; Smith 2011).

Relevant laws and guidelines:
Biospecimens obtained for research in Australia can be sent overseas for research. HRECs are expected to either approve individual overseas research projects or be satisfied that the tissue will be used only in a manner consistent with the original consent. According to the NHMRC *National Statement,* consent to biobanking needs to include: "whether their biospecimens and associated data may be distributed to other researchers, including those outside Australia."

The *National Statement* specifies that international samples and data can only be used in Australia if they have been collected in a manner consistent with requirements described in the *National Statement* and relevant Australian legislation. In addition, the NHMRC *Code for the Responsible Conduct of Research* states that researchers supported by Australian public funding should make every effort to comply with Australian policy when conducting research outside Australia. Any deviation from the Code must be submitted for institutional approval.

2.1.3. "Big data" research

While big data research increases the capacity to make fine comparisons, identify rare events, deal with population variability and in so doing identify potential molecular targets for multifactorial diseases, it also exacerbates a number of ethical concerns associated with databank research (Lipworth et al 2017). With respect to privacy, for example, big data analytics have reached a level of sophistication that makes it impossible to promise perfect anonymity, even if all identifiers are removed from a particular segment of data (Scaiano et al 2016). Data are also collected continuously, in bulk, in a granular way, and are acted on rapidly, which can increase both the likelihood of, and risks associated with, loss of confidentiality (Erdmann 2013; Frizzo-Barker et al 2016; Schadt 2012; Terry 2012).

Dilemmas regarding return of incidental findings is also magnified in the context of big data research, which is more likely to generate incidental findings simply by virtue of its scale. Matters are complicated further by questions about the validity, reliability, and utility of the results of big data research (including, but not limited to incidental findings). For example, the majority of the information on genomic variants may be of unknown clinical value and may mislead clinicians and patients as to its pathogenic potential (Fischer et al 2016; Manrai, Ioannidis and Kohane 2016; Shoenbill et al 2014). And participants' ability to control their data and withdraw from research is complicated by the challenges associated with erasing and 'forgetting' big data (Newman 2015).

There are also technical challenges associated with the analysis of big data. Some of these are well-recognised statistical challenges that apply to any kind of observational research (such as managing biases and confounding factors), but others relate specifically to machine learning and other emerging big data analytics. Importantly, these technical issues have ethical implications. For example, the complexity of analytic models and predictive algorithms may limit the capacity for the public, and even experts, to interpret and question research findings, which may lead them to act on false predictions (Dereli et al 2014;

Fischer et al 2016; Vayena et al 2015). People may also lose sight of ethically important contextual nuances that are obscured by big data analyses (Boyd and Crawford 2012; Busch 2014; Mittelstadt and Floridi 2016).

2.2. Clinical trials of targeted therapies

Once a potential target for a precision medicine has been identified, and a corresponding drug has been produced, it is necessary to assess its safety, efficacy and cost-effectiveness. For common diseases, or rarer diseases in which most or all patients express the relevant molecular target, clinical testing follows the same path—and raises the same ethical issues—as that used to generate evidence about any other therapy. In many cases, however, clinical trials of targeted therapies are complicated by (among other things) the rarity of the disease or molecular target; the need to simultaneously test therapies and companion diagnostics; and the ethical imperative to allow biomarker positive patients to crossover to active treatment if their disease progresses during a trial. These challenges make it difficult to generate robust evidence of efficacy and safety, and to generalise the findings of trials to patient populations (Lewis, Lipworth and Kerridge 2014; Lewis et al 2013).

In response to these challenges, the traditional phases of clinical research are becoming increasingly blurred, and new study designs—such as double randomisation, single arm studies, n=1 studies and adaptive and pragmatic trials—are being devised. While these trials are believed to be ethically advantageous in some ways (for example, better accommodating clinical equipoise and informed consent, and reducing patients' chances of being exposed to sub-optimal treatment), they raise their own ethical issues (Hey and Kimmelman 2015). While it is beyond the scope of this chapter to consider the ethics of these emerging trial designs in detail, one key issue is that there may not be a state of genuine equipoise when patients enter trials (that is, those conducting trials may not be entirely agnostic as to whether patients are likely to benefit from the intervention being tested), or studies may continue beyond the point at which equipoise has been lost. A related ethical issue is that many patients enter these trials not (only) to contribute to research, but as a means of gaining access to targeted therapies. This turns on its head the ethical assumption that patients need to be disabused of any "therapeutic misconception" when they decide to participate in research (Meurer, Lewis and Berry 2012).

2.3. Observational studies of targeted therapies

New clinical trial designs go only part of the way to solving the problems of evidence generation for precision medicine and, as a result, there is an increasing emphasis on evaluating targeted therapies in the 'real world' using observational research. Because these kinds of studies require collections of data about safety and efficacy, the ethical issues they raise are essentially the same as those raised by databank research. As described in Section 2.1, the susceptibility of individuals' health data to breaches of privacy raise key ethical issues around collection, storage, and linkage practices. While, in both settings, the data used in research might be collected primarily for research purposes or for other—such as clinical or administrative—purposes, clinical studies of targeted therapies almost invariably entail the "secondary use" of data collected for clinical or administrative purposes. In this context, consent bias can be a major problem where studies seek to assess the survival of a particular group of patients for future comparison with newer trseatments in similar clinical settings. Assessment of survival is also likely to be confounded if data can only be collected from living patients. Although surviving relatives may assist with data collection, this can be challenging for logistical and emotional reasons (Lewis, Lipworth and Kerridge 2017).

3. The ethics of regulating and funding targeted therapies

3.1. Regulatory challenges

The challenges associated with generating evidence about targeted therapies affect not only clinical researchers, but also regulators, who need to determine whether these therapies are sufficiently safe and efficacious to justify market entry. The key questions here is whether, and to what extent, usual standards of evidence—based on large Phase III randomised trials—should be adjusted for targeted therapies.

As long as these standards remain in place, patients seeking access to targeted therapies either need to rely on their clinicians to prescribe such therapies off-label or seek compassionate access from pharmaceutical

companies. While these mechanisms provide much-needed access to targeted therapies for some patients, they raise their own ethical issues in that they tend to be ad hoc, inequitable, and, in many cases, driven more by compassion and desperation than by evidence (Ghinea, Lipworth and Kerridge 2015; Lewis, Lipworth and Kerridge 2017; Lewis et al 2014).

In part as a response to the problems with off-label prescribing and compassionate access, there is currently a large push internationally for accelerated regulatory approval of targeted therapies, whereby regulatory standards are reduced in order to facilitate 'timely' market entry. The problem with such programs is that they generally create a disincentive for companies to gather high-quality, standardised data, and for patients to participate in trials. This is not just an epistemic issue but also a moral issue because it compromises the altruism and social solidarity that form the basis for participation in research. It also has the long-term effect of creating sustained uncertainties and placing patients at risk. In this regard, it is morally significant that medicines-including targeted therapies—approved through accelerated access schemes are more likely to have health warnings related to unanticipated toxicities and more likely to be subsequently withdrawn from the market (Pace et al 2017a; Pace et al 2017b; Pace et al 2017c).

Supporters of accelerated regulatory approval processes for targeted therapies often counter that, once products are on the market, 'real world evidence', will be generated in order to determine whether they are sufficiently safe and effective to remain on the market. The problem with this 'solution' is that companies have little incentive to conduct research that could result in withdrawal of products from the market and, even if they do, patients may be exposed to risk for considerable periods of time before products are withdrawn (Pace et al 2017a; Pace et al 2017b; Pace et al 2017c).

Relevant laws and guidelines:
The *Therapeutic Goods Act 1989* (Cth) plays a crucial role in regulating the supply of health-related products in Australia. The Act is administered by the Therapeutic Goods Administration (TGA), and regulates the introduction of therapeutic goods into the Australian market. Drugs must satisfy rigorous pre-market assessment standards prior to marketing approval, requiring evidence of clinical utility, safety and efficacy through clinical trials approved and monitored by Human Research Ethics Committees (HRECs). Fast track registration may be allowed in limited circumstances where there is unmet clinical need. For devices, including companion diagnostic genetic tests, which are classified as in vitro devices (IVDs), the stringency of pre-market assessment depends on risk classification.

3.2. Funding challenges

The complexities of funding targeted therapies and companion diagnostics are described in detail in Chapter 7. From an ethical perspective, targeted therapies have two main advantages. First, targeting treatments to those patients who are most likely to benefit and who are least likely to be harmed can be a more cost-effective and less wasteful approach than funding treatments developed and tested on heterogeneous populations. Second, targeted therapies often provide options for subsets of the population who have few options available to them—funding these therapies is, therefore, a way of promoting equity.

The problem is that, as is the case with orphan medicines used to treat rare diseases, the companies that produce targeted therapies often charge large sums of money per patient in order to make a profit. Where resources are limited, this inevitably creates opportunity costs, depriving other patients of interventions that they need or want. This is not necessarily a problem if the targeted therapies being funded are known to be highly effective and costs can be offset through savings elsewhere, but this is not always the case (Lewis, Lipworth and Kerridge 2014; Lewis et al 2013).

In this regard, a key moral challenge for payers is that, while a subset of patients is likely to respond very well to any new targeted therapy, the science of precision medicine has not yet reached a point where it is always possible to predict in advance who these patients will be. This means that enormous sums of money need to be spent on treating patients who are unlikely to respond in the hope of helping the few who will. A related challenge is that new targeted therapies are seldom used in isolation, and even with the strongest

evidence from trials it is difficult to assess their likely benefit (and therefore cost-effectiveness) in real world practice. Of course, none of these economic nuances matter to patients who are desperate for access to treatment, or who or believe that they have a "right" to access therapies, and who can make strong moral claims for subsidised therapies that can provide even the smallest chance of the smallest benefit (Ghinea, Little and Lipworth 2017; Harper, Ghinea and Lipworth 2017).

Like regulators, payers are under increasing pressure to facilitate early subsisidation of targeted therapies that have not (yet) been demonstrated to be cost-effective. These programs are referred to as "coverage with evidence development" or "managed entry" schemes. The ethical and socio-political advantages of such programs are that they: "balance the interests of clinicians and patients, who want early access to new diagnostic tests and medicines; payers, which want to address genuine health needs but do not want to pay more for medicines than they are worth; and pharmaceutical companies, which want to be paid fairly for their products" (Lewis, Kerridge and Lipworth 2015: 4114). These programs, however, raise similar ethical issues to those associated with accelerated regulatory approval programs, as well as additional issues related to: the need to pay for therapies while evidence is being developed; the barriers to enrolling patients in research when subsidised access is otherwise possible and equipoise cannot be assured; and the psychological distress and inequities that might be a feature of efforts to "disinvest" from subsidised therapies (Lewis, Kerridge and Lipworth 2015).

4. The clinical application of precision medicine

Precision medicine has significant potential to help both individuals and the public by generating more efficient care pathways, facilitating access to new and more efficacious treatments, and enhancing the ability to intervene early in disease progression. However, while noting the potential benefits of targeted therapies, it is also important to ensure that hype and scientific hubris do not permeate the clinical space. Like all medicines, targeted therapies can harm as well as help patients, and clinicians need to be just as alert to risk-benefit ratios when prescribing targeted therapies as they are when considering any kind of intervention.

4.1. Genetic and genomic testing/molecular diagnostics

The clinical application of precision medicine entails either targeted molecular testing, or omic sequencing, in order to determine whether a patient expresses a pharmacologically relevant molecular target. When the tissue being tested is diseased (for example tumour tissue), few ethical issues arise as the tissue makeup is not considered predictive of any other traits. When, however, healthy tissue is tested or screened (such as non-tumour tissue in a patient with cancer) or an entire genome is sequenced in the pursuit of an isolated genetic abnormality, the ethical issues are very similar to those that arise in the context of genetic or genomic research, including risks to privacy and associated discrimination (for example difficulties in obtaining life insurance) and the management of findings of uncertain clinical significance and incidental findings (See section 2.1).

Other issues that arise particularly in the clinical setting include the potential for information from genetic/genomic tests to impact upon family members and future generations and, increasingly, the quality of direct-to-consumer and point-of-care genetic and genomic tests (Vogenberg, Barash and Pursel 2010). One issue that perhaps distinguishes testing for diagnostic purposes and testing for the purposes of guiding precision medicine is that the latter might threaten patient autonomy if, for example, public or private insurers begin to coerce patients into having genetic tests as a condition for coverage of medicines (Vogenberg, Barash and Pursel 2010).

Confidentiality and discrimination

The collection and testing of patient samples in the clinic raises the risk that their data, including that derived from tissue samples, may be accessed by unauthorised parties. Such breaches of confidentiality are particularly concerning when they lead to the release of genetic information, both because genetic data is always potentially re-identifiable (Chalmers, Nicol and Otlowski 2014) and because genetic information can

be both diagnostic and predictive, both personal and familial, and of both immediate and future relevance to individuals (Otlowski and Eckstein In Press). While processes for protecting the confidentiality of data are constantly evolving, the reality is that, as mechanisms for data protection become increasingly sophisticated, new strategies inevitably emerge that undermine whatever protections exist (Erlich and Narayanan 2014; Gymrek et al 2013).

Individuals who are discovered to be at risk of certain diseases, or carriers of deleterious genetic variants, can find themselves vulnerable to discrimination by, for example, insurers or employers (Barlow-Stewart and Keays 2001; Taylor et al 2008). While health insurance in Australia is community rated, under an exemption provided by the *Disability Discrimination Act 1992* (Cth), life insurance is based on individual risk assessment and applicants are required to disclose all relevant health information including any genetic test results. The stance taken in Australia with respect to insurance is in marked contrast to the position taken by many European countries that have legislated to prohibit life insurers from using genetic test information (Otlowski, Taylor and Bombar 2012). In recent years, there have been growing calls to restrict life insurers' access to genetic test information, partly on the grounds that genetic discrimination may discourage people from participating in both genetic testing and genetic research (Keogh et al 2017).

Even where clinical data remains sufficiently aggregated or anonymised that individuals cannot be identified, there is still the potential for group-level harm in the form of profiling, stigma and discrimination (Clark, Barney and Reddington 2016; Rothenberg and Wang 2006).

Relevant laws and guidelines:

The legislative regime for the protection of privacy is particularly complex in Australia because of our federal system of government and the limitations on federal legislative power imposed by the Constitution. As a result, there are both federal and state-based privacy statutes. State-based laws govern the privacy of information held by state government agencies, which include public hospitals and many universities. The federal *Privacy Act 1988* (Cth) (*Privacy Act*), in contrast, governs federal government agencies and corporations, subject to certain exceptions. To add a further layer of complexity, until 2014 different obligations were imposed on federal government agencies, through a set of *Information Privacy Principles*, and corporations, through the *National Privacy Principles*. The *Privacy Amendment (Enhancing Privacy Protection) Act 2012* (Cth) created a new uniform set of *Australian Privacy Principles* (APPs). Primarily, the APPs create obligations relating to the collection, storage, use and dissemination of, and provision of access to personal information.

There is, however, still a lack of national consistency in Australian privacy laws. Another problem is that the current federal regime is focussed on the protection of information and records, so genetic samples are currently not protected even though they potentially hold a substantial amount of information about the individual concerned (Otlowski 2013). Additionally, enforcement mechanisms available under the current regime are weak and what protections do exist are lost once information is outside jurisdictional boundaries. The Australian federal parliament is currently considering whether to approve an amendment to privacy legislation that would make it a criminal offence to re-identify de-identified government data. Whilst not directly relevant to personal genetic data, this illustrates the seriousness with which the federal government views the protection of privacy.

In 2014, guidelines were introduced to regulate the disclosure of relevant genetic information to genetic relatives, even without the consent of the index patient (National Health and Medical Research Council 2014b). These guidelines do not create a duty to disclose relevant information to a genetic relative without the consent of the patient; rather, they provide protection from such disclosure breaching the *Privacy Act*, provided that the guidelines have been closely followed. Although representing an important step forward, these guidelines do not cover health practitioners working in state-based public hospitals. To date, only New South Wales has introduced equivalent state legislation through the *Health Legislation*

Amendment Act 2012 (NSW), amending the NSW *Health Privacy Principles* to make them consistent with the federal guidelines (Otlowski 2015).

Another issue that is particularly relevant to clinical precision medicine is the regulation of genetic tests. It is prohibited in Australia to make available to individuals genetic test kits for self-testing for the presence of or susceptibility to serious diseases. However, foreign providers of genetic tests who make their services available directly to consumers through the internet are not regulated through this legislation. The NHMRC has produced an information resource for consumers (National Health and Medical Research Council 2014c) as well as more general statement cautioning about the use of direct to consumer genetic testing (National Health and Medical Research Council 2014a)

Return of Results and Incidental Findings

Often in the course of clinical care, particularly where genomic testing is employed, information emerges that is not directly related to the question being asked but that has potential clinical significance. The quandary here for clinicians is that, while informing participants of such findings might enable them to prevent disease or respond more rapidly when symptoms arise, the significance of findings is not always clear; and people might prefer not to receive such information no matter how clinically 'significant' it might be (perhaps because of the insurance implications discussed above) (McGuire et al 2013; Wolf et al 2012).

4.2. Big data and predictive analytics in the clinic

While it might seem on the surface that targeting therapies to individual patients can only improve clinician—patient relationships and facilitate the more general pursuit of personalised medicine, the reality is more complex. For example, it is not at all clear that doctor-patient relationships, and the overall patient-centeredness of care, will be enhanced by the presence (even in the background) of artificial intelligence machines. There are also other ethical challenges associated with bringing big data and predictive analytics into the clinic including:

1. consent—do patients need to be told that their care is being shaped (including resources being allocated) by predictive algorithms?
2. liability—who is responsible for model failures or for failure to follow a predictive model's recommendation? and
3. autonomy—can machine-generated decisions be overridden on the basis of individual preferences? (Cohen et al 2014; Obermeyer and Emanuel 2016).

5. Equity

Thus far this chapter has focused on the wellbeing of those people who are fortunate enough to be invited to participate in research studies of targeted therapies; to live in countries where targeted therapies are subsidised; and to have access to the clinical services through which these therapies might be offered. The reality, however, is that the benefits and risks of precision medicine are not distributed evenly either within or between populations.

5.1. Equity in precision medicine research agenda setting

Much attention has been paid to the capacity for targeted therapies to revolutionise the treatment of monogenic disorders, rare diseases and rare subsets of more common diseases (for example molecularly defined cancers). While there is nothing trivial about these endeavours, it is important not to assume that the targeted therapies being developed correspond to the greatest areas of unmet need in the community. To this point, it is important to note that precision medicine has not yet addressed many common diseases that may have important social and environmental determinants. This is partly because the science is not yet well enough developed to deal with their multigenic complexity, but it is also because science is less adept at responding to social challenges that may determine health--such as poverty, famine, inequity—than it is at identifying and responding to physically tangible cellular and molecular change.

Thus, while research in genomics and the pursuit of precision medicine is laudable, it is important that this does not occur the expense of measures to address national and international social and political determinants of health (Savard 2013). It is also important that precision medicine initiatives themselves focus on areas of genuine unmet need (Pang 2009). These issues are particularly salient in Australia given the parlous state of the health of indigenous Australians and other vulnerable groups. As noted in Chapter 5**,** precision medicine has the potential to "close the gap" in indigenous health, but only if the diseases it targets are those that affect the most disadvantaged groups.

5.2. Equity of access to subsidised targeted therapies

Even if targeted therapies are relevant to the health needs of disadvantaged populations, this does not mean that access to these therapies will be equitable. In many countries, the price of targeted therapies is well above the median salary, and because these countries are struggling to establish systems for universal health coverage, these medicines are currently available to only the wealthiest people (Alyass, Turcotte and Meyre 2015). In this regard, it is noteworthy that it is in these countries that many targeted therapies are tested—such as imatinib for the treatment of chronic myeloid leukaemias—and those who participate in trials do not have subsequent access to ongoing therapy.

Even in high income countries, such as Australia, where there are national systems for subsidisation of medicines that are known to be effective and cost-effective, the high cost of many targeted therapies is already placing a massive strain on resources. Furthermore, even if people live in countries that give them access to subsidised targeted therapies (that the country can afford), it cannot be assumed that these therapies will be accessible to disadvantaged groups, such as Indigenous Australians and those living in rural and regional locations who may lack access to clinical services.

A commitment to equity requires developing precision medicines in a manner that is consistent with international ethical standards regarding care for local communities, care for research participants and access to therapies for research participants beyond the period of clinical trials. A commitment to equity also requires constant review and reform of health systems, and a political commitment to universal coverage and access. This, in turn, demands explicit recognition of the globalisation and networking of research, which creates social and ethical obligations that cross national borders.

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