Chapter 4. Developing public health genomics to strengthen preventive care in Chile

A well-designed national strategy on using public health genomics to strengthen public health and preventive care could make Chile a regional leader in this emerging field. Although the global trend of increasing use of genomic testing improving diagnosis and treatments for the sick and preventive measures for the healthy, Chile lacks of a national plan for implementing precision medicine in the clinical practice or public health policies. International efforts in OECD countries can provide good examples of government-industry system structures that have been successful in the expansion of genomics services, particularly for informing public health and preventive care. Regulation, rigorous empirical evidence, development of the genetics workforce, genetics education for health professionals and the public as well as careful attention to equitable service design is necessary to achieve widespread public health and preventive care applications in Chile.

4.1. Introduction

A number of public health priorities in Chile have the potential to benefit from wider application of precision medicine. From a public health and preventive care point of view, precision medicine is most likely to offer benefit in those conditions which generate a sizeable burden of disease; which have a significant inherited component; and whose prevention, early diagnosis or management could be influenced by knowing the genetic associations in a given individual or community.

In choosing to engage, at this stage, with the role of precision medicine and public health genomics in health and disease, Chile is showing a clear understanding of the potential for genomic science to both benefit and transform the field of preventive medicine. Taking steps to consider the role of precision medicine for public health care at this point should leave Chile well-prepared for the rapid ongoing expansion of available genetic tests.

This chapter discusses, firstly, the potential for public health genomics to improve public health and preventive care in Chile, including the challenge of combining genetics information with environmental and behavioural risks. Secondly, the chapter examines the current precision medicine services in Chile, and current plans to develop clinical genetics and services. Finally, the chapter makes a series of recommendations for ways in which Chile could accelerate the provision of precision medicine and public health in a sustainable, equitable way.

4.2. The potential for clinical genetics and genomics to improve public health and preventive health care in Chile

This chapter discusses the potential of public health genomics to improve public health and preventive health care in Chile. Other important applications of genomics such as therapeutics are considered where appropriate and relevant.

4.2.1. Precision medicine and public health genomics

The completion of the Human Genome Project in 2003 has dramatically increased our understanding of the role of genes and their influence on health and the biological mechanisms of disease (Green, Watson and Collins, 2015[1]). Over the last two decades – in a context of scientific and technological advancements – the concept of precision medicine has emerged as a new approach that takes into account variability in genes, environment, and lifestyle factors to determine individual risk of disease, and design optimal prevention and treatment strategies.

The field of genomics can be understood as the study of all of an organisms' genes and relationships between the genes; genetics addresses the functioning and composition of a single gene (WHO, 2016). In health, genomics is being used in different ways, including around screening, testing, therapeutic development and treatment, policies and research, related to the human genome. The National Human Genome Research Institute in the United States defines genomic medicine as follows: "Genomic medicine is an emerging medical discipline that involves using genomic information about an individual as part of their clinical care (e.g. for diagnostic or therapeutic decision-making) and the health outcomes and policy implications of that clinical use." (National Human Genome Research Institute, 2016). Public Health Genomics has been understood as the integration of genomic-based knowledge into public health policy and population health (Boccia

et al., 2009; Bellagio Statement, 2005; Burke et al., 2006). For example, public health genomics could include the integration of population-based information on genetic variation and gene-environment interactions to develop stronger health improvement and disease prevention. There are a number of common terms in the field of genomics, including precision medicine, stratified medicine, and genetic counselling (see Box 4.1).

Along with the term public health genomics, this chapter primarily uses the terms 'precision' medicine, in particular following the definition established by the United Kingdom's Programme Coordination Group, and repeated in the OECD's 2017 publication on New Health Technologies: "[refining] our understanding of disease prediction and risk, onset and progression in patients, informing better selection and development of evidence-based targeted therapies and associated diagnostics. Disease treatment and other interventions are better targeted to take into account the patient's genomic and other biological characteristics, as well as health status, medications patients are already prescribed and environmental and lifestyle factors" (Innovate UK, 2016) (OECD, 2017[2]).

Box 4.1. Genomics and public health genomics – key terminology

There are a number of commonly used terms in the field of genomics, including precision medicine, stratified medicine, genomic medicine, or personalised medicines, some of which are equivalent.

Precision medicine is relates to the tailoring of therapies and interventions based on a patient's genomic and other biological characteristics (which can include health status, existing medications, environmental and lifestyle factors) ((Phillips et al., 2014[3]); OECD, 2016; Innovate UK, 2016). Precision medicine can be used as an all-encompassing term that includes more specific terms, including personalised, stratified, and genomic medicine. Personalised medicine is a widely used term, but has been criticised for the suggestion that it entails the development of unique therapies designed for each individual, and amongst experts a preference for more specific terminology has emerged (Doble et al., 2017). **Genomic medicine** is the use of genetic information (for instance gleaned from genomic sequencing) to a determine individuals' disease risk, diagnosis, and treatment. Genomics addresses all genes and their inter relationships, while genetics scrutinizes the individual gene, its composition and functioning. **Genetic testing** looks at an individual's genetic code to identify changes – variants or mutations – which could indicate health conditions. Until recently genetic testing has been performed on a small number of known genes, for example analysis of genes known for determining certain cancer risks (for example BRCA1 and BRCA2), but recent developments have made it possible to rapidly sequence far larger amounts of DNA (Phillips et al., 2014[3]).

'**Sequencing',** which is also referred to as **next-generation sequencing (NGS), parallel or high-speed sequencing** refers to a number of different modern sequencing technologies to sequence DNA and RNA much more quickly and cheaply than before. Sequencing includes targeted sequencing which targets one or two genes, including as a panel of multiple genes, whole exome sequencing which involves the DNA sequencing of the exome (about 1% of the genome), and whole genome sequencing (WGS) which entails the sequencing of the entire genome (about 22 000 genes) (Phillips et al., 2014[3]) (OECD, 2016; Doble et al., 2017).

Stratified medicines refers to the grouping of patients based on their disease risk or

likely responsiveness to treatment, based on the use of a biomarker diagnostic test to determine the target population (a biomarker is a biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease) (Doble et al., 2017[7]; OECD, 2016). Such a test is used to identify before or during treatment patients who are most likely to benefit from the corresponding medical product or patients likely to be at increased risk of serious adverse reactions. Biomarker diagnostics include single tests to establish risk or disposition to treatment, or as increasingly the case, multiplex tests testing several biomarkers simultaneously.

Genetic counselling can be used to understand an individual's disease risk, based on their family history, and an understanding of different hereditary risks, and patterns of genetic transmission. Genetic counselling does not need to involve genetic testing.

Precision medicine is also an exploding field. Since 2003 and the mapping of the human genome the availability of genetic testing has grown rapidly; recent estimates suggest that there are currently 75 000 genetic tests on the market, and a further 10 are appearing on a near-daily basis (Phillips et al., 2018[4]). While developments in the field of genomics are potentially game-changing for patients – a recent study found that between 2013 and 2017, 48% of FDA-approved precision medicines could be considered 'breakthrough therapies' (Pregelj et al., 2018[5]) – these new and rapid developments nonetheless pose new challenge for health policy makers, many of which this chapter seeks to explore.

4.2.2. Precision medicine can be used as a powerful diagnostic tool

Precision medicine can be used as a powerful diagnostic tool. One of the most widespread uses of genomic testing is to identify congenital abnormalities and diagnose other conditions. Between two to three per cent of children are born with a major congenital abnormality, Of these, around one third will have a genetic component such as Trisomy 21 (Down's Syndrome). The identification of the underlying genetic cause is important to understand prognosis, guide treatment decisions, and support parents when considering having additional children. A very small number of these genetic cases (less than 5%) may be detected by one of the oldest and most basic genetic tests, karyotyping. Karyotyping simply involves examining the number and morphology of chromosomes in a cell using a light microscope.

Improving the detection rate of other genetic components for major congenital abnormalities – which again can guide treatment decisions and help parents when considering having additional children – requires more sophisticated tests, such as molecular karyotyping (where DNA probes are labelled with fluorescent tags, for example). In addition, full sequencing of all genes that have been previously associated with diseases can now be performed simultaneously by Next Generation Sequencing – a technology that allows the rapid sequencing (i.e. determining the order of the DNA building blocks) of large amounts of DNA. Negative results can be further studied by extending sequencing to all genes in the genome (i.e whole-geome sequencing). Such newer techniques can increase detection rate by up to 30%. Whole-genome sequencing for example can be a vital tool for establishing diagnosis when previous targeted test has failed, and some studies have shown it to be cost effective (Nambot et al., 2018; Walsh et al., 2017; Valencia et al., 2015).

4.2.3. Newer genomic technologies may advance preventive health care and public health more broadly

At this point, common diseases including, but not limited to, cancers and many cardiovascular diseases, have been found to be vastly more genetically complex than was first anticipated. Considerable investments have been made in investigating the role of genomics in common cancers, for instance Lynch syndrome or Breast cancer susceptibility genes (BRCA) 1 and 2 for breast cancer.

Sequencing (for example, targeted sequencing, whole exome sequencing or whole genome sequencing, see Box 4.1) can be very valuable in paediatric disorders, where clinicians are searching for a diagnosis with very little sense of where to look. For example, Next Generation Sequencing (NGS) makes it possible to compare one individual's genes' with a panel of genes from close relatives to look for possible indicators of rare diseases.

In terms of public health, the value of genomics is evident when tests can provide reliable information on individual risk of disease, which in turns can inform the design of targeted prevention strategies at the population level. For instance, using genomics to identify people carrying genetic mutations that predispose them to a very high risk of developing colorectal or breast cancer can allow screening programs to offer more aggressive screening and surveillance regimen to these groups. (Pashayan et al., 2013). Furthermore, it is plausible that this increased precision could offset other unnecessary tests and yield cost savings.

4.2.4. Applied genomics could bring benefits to a number of Chilean public health priorities

From a public health and preventive care point of view, genomic testing is most likely to offer benefit in those conditions which:

1. generate a sizeable burden of disease (whether measured in terms of mortality, morbidity or cost);
2. have a significant inherited component; and/or whose prevention, early diagnosis or management could be influenced by knowing the genetic associations in a given individual or community.

These criteria apply to cancers where, for example, 10-20% of cases may have a hereditary component.

Another area of potential benefit from genetic testing relates to congenital anomalies. Around 2-3% of children are born with a major congenital abnormality, which represents approximately 7 500 births in Chile each year. Around a third of these anomalies will have a significant genetic component. Identification of any genetic basis has a potentially important preventive aspect, because parents' family planning may be influenced by understanding the risk of having further children affected by the condition. Achieving a molecular (genetic) diagnosis also has public health implications, given the money potentially saved by avoiding a prolonged "diagnostic odyssey". Examples would include the lysosomal storage disorders (such as Gaucher's disease) whose treatment in Chile is currently funded through the Ricarte Soto Law.

Genetic testing is currently less relevant to other major public health concerns in Chile, such as obesity. While genetic testing around obesity is a compelling area of research, at present the identified genetic variants associated with obesity and overweight are so

strongly eclipsed by environmental and behavioural factors that genetic information has little predictive value. Other conditions, such as some forms of lymphoma, have stronger genetic associations, however for these conditions there is limited knowledge about how to translate awareness of the genetic antecedent(s) to a public or preventive care strategy.

4.2.5. Combining genetic information with environmental and behavioural risks

The public health challenges Chile faces, like other OECD countries, are dominated by non-communicable conditions, which tend to have a complex natural history and aetiology. That is, genetics offers only part of the information to complete a complex picture of disease risk.

Ischaemic Heart Disease (IHD) for example, has a hereditary component which may be revealed by genetic testing, however alone, this information is less predictive than blood pressure, blood cholesterol or body mass index at determining IHD disease risk (Howson et al., 2017; Khoury, Iademarco, & Riley, 2016). Further, social, cultural and environmental determinants cannot be revealed through genetic testing, and the expression of a hereditary tendency towards high blood pressure for instance may be influenced (to an extent) from building healthy workplace and community environments. Thus in the case of IHD, to determine risk and identify preventive approaches, genetic information needs to be combined with phenotypic information, as well as broader socio-cultural information to be used effectively.

Screening for some cancers can be informed by genetic information if biomarkers are used to target programmes to those at greatest risk of developing particular forms of cancers. This can improve both efficiency and early detection, minimise adverse events, and may assist in personalising treatment options if a cancer diagnosis is made (Chief Medical Officer, 2017).

4.3. Current clinical genetics and genomics services in Chile

4.3.1. Chile benefits from a specialist clinical genetics workforce, although it is small by international standards

There are currently 33 clinical geneticists working in Chile, equivalent to roughly 1 geneticist per 650 000 inhabitants (Superintendencia de Salud, 2018[6]). Clinical geneticists are required to do a three-year post-graduate residency, and be formally registered with the Superintendency of Health to offer specialist care. There is currently one post-graduate residency programme available in Chile, with around 7 students enrolled. In addition to clinical geneticists, some oncologists (cancer specialists) also offer genetic screening—for the common translocations that are associated with leukaemia, for example. A small number of paediatricians and/or obstetricians specialising in foetal medicine and pre-natal care may also offer relevant genetic tests to potential parents.

Around three quarters of clinical geneticists in Chile are located in Santiago. The unequal distribution of this workforce may be less of a problem than in other specialities, since clinical genetics lends itself well to being provided through telemedicine. All work is conducted in both the private and public sectors.

There is, however, a shortfall in specialist numbers, according to international comparisons. Several OECD health systems employ three or more clinical genetics consultants per million population (and some, such as Norway and Finland, have more

than five). By comparison, in 2013 there was one geneticist per 120 000 population in England, 1 per 196 000 in France, one per 176 000 in Finland and 1 per 90 000 population in Norway (The European Society of Clinical Genetics, 2013). Comparatively Chile is lacking at least half the specialist workforce it needs. Furthermore, Chile currently does not have any recognised genetics counsellors. These are individuals trained in explaining genetic risk to patients, combining this information with knowledge of an individual's behavioural, social and environmental risk, and helping them make decisions (regarding starting a family, for example, or prophylactic surgery) based on that information. Plans are underway however, to develop this workforce, and some qualifications are already offered even if they are not accredited as a medical speciality. For example, the medical faculty at the University of Chile (MEDICHI) offers a diploma in genetic counselling.

4.3.2. Genetic services offered in Chile

At least six institutions in Chile currently offer genetic testing services, including the Laboratorio de Biología Molecular y Citogenética at Pontificia Universidad Católica (LBMC-PUC), the Centro de Genética y Genómica at the Universidad del Desarrollo (CGG-UDD), the Laboratorio Clínico de Biología Molecular, Hospital del Salvador (LCBM-HS), the Instituto de Nutrición y Tecnología de los Alimentos at Universidad de Chile (INTA-UCH), Universidad del Desarrollo (UDD), and Genética Molecular, Laboratorio Biomédico, ISP (GMLB-ISP).

There are a few companies that are currently offering genomic services in Chile, both for the research and clinical practice. However, all these companies are international, and send samples abroad for sequencing and data analysis.

Some domestic laboratories offer genomics services, all of which function within research institutions, in particular out of universities. Namely, INTA-UCH and CGG-UDD offer gene expression profiling, genotyping and molecular karyotyping by microarray technology. GMLB-ISP, LBMC-PUC, LCBM-HS and CGG-UDD are the only laboratories certified for clinical services that have NGS capabilities, but as yet no genomic services for the clinic with this technology, except for microbial genetic typification done by GMLB-ISP. For research applications, Austral-omics at Universidad Austral offers sequencing of gene panels and the ChileGenomico Laboratory at the Universidad de Chile can sequence gene panels, transcriptomes, and whole exomes. Despite these institutional efforts, there is no national network of genomic services, and due to high costs for the average patient, the demand for genomic services remains restricted to the high-income fraction of the population. However, the presence of these nodes of technological and human-capital development in genomics creates an opportunity for broadening the availability of genomic medicine when conditions improve and demand increase.

4.3.3. Very few precision medicine services are covered by the public insurance system, leading to access inequalities

There are two clinical genetics services currently covered by FONASA, both falling within the sphere of cytogenetics: i) karyotyping (for chromosomal abnormalities, such as trisomy 21 (also known as Down's syndrome); and, ii) Fluorescent in situ hybridization (FISH), used to detect specific DNA sequences that are associated with some congenital syndromes (such as Prader-Willi syndrome) and some leukaemias. Newborn screening for phenylketonuria (always genetically determined) and congenital hypothyroidism

(sometimes genetically determined), is also well-established, and there are plans to expand testing. There are no molecular genetics or genomic analyses offered within the public insurance system. Furthermore, because private insurers take their cue from the public system, no molecular genetics or genomic analyses are generally offered by ISAPRES either. This means that only those who can afford to pay out-of-pocket for private consultations and testing in independent laboratories can benefit from newer technologies.

The importance of access to more advanced genetic tests and analyses can be illustrated by considering the proportion of children born each year in Chile with a major congenital abnormalities—several thousand in number. Only a small minority (less than 5%) of genetic causes can be detected through the cytogenetics currently on offer. Detection rates for these congenital conditions increases by 20-30% with more advanced techniques offered by molecular genetics, including genome sequencing. However, only parents concerned about inherited conditions in their children can receive genetic testing and counselling in the private sector. In exceptional cases (where the child's life depends on a molecular diagnosis of their disorder), FONASA may cover costs. But in most cases, parents will have to pay around USD 2 000 out-of-pocket for genetic tests more advanced than those currently offered in the public system.

Furthermore, there are several clinical conditions (notably several cancers), with an important genetic component that are included within the GES but where genetic testing is not covered. The Ricarte Soto Law (see also Chapter 1) established coverage for some rare inherited diseases, including some lysosomal storage diseases (such as Fabry's or Gaucher's disease), other inherited disorders of metabolism (such as tyrosinemia), and HER2+ breast cancer. As of 2018 more than 10 000 people had benefited from the Law's provisions. Although there are some exceptions, for example molecular testing is covered for women with suspected Fabry's disease, for many thousands of patients GES manifests a discord: treatments are offered, but genetic testing that could offer a quicker and more precise diagnosis is not. Independent genetics laboratories report a 10-15% annual increase in demand in recent years illustrating the size of unmet need in this area.

While not necessarily addressing financial access difficulties, telemedicine has played a significant role in reducing barriers associated with geographical access to genetic specialists and services. Indeed, genetic consultations held through videoconferencing is common and patients reported high levels of satisfaction with telegenetics in general (Iredale, Hilgart, Hayward, & Coles, 2012). Beyond patient interactions, telegenetics is also common between professionals with genetics labs often located a distance away from health services where data may be interpreted or stored, as in the case of the 100 000 genomes project in the UK.

Finally, public-private partnerships have supported the majority of developments and advancements in clinical genomics services in other OECD countries. For instance, the WGS project in Australia is supported by a range of public and private organisations including not-for-profit organisations. For the US, genomics development has involved pharmaceutical companies. Similarly, although the UK genomics initiative (100 000 Genomes Project) is based in the NHS and thus is publicly funded, private input is also evident through research organisations as well as pharmaceutical companies and the same is true for Canada (Genome Canada, 2017; Genomics England, 2017). Such public-private partnerships do not currently exist in the precision medicine field in Chile. The state has invested in a handful of small-to-medium size private initiatives to implement genetic testing in health For example, the Government of Chile partially funded the

creation of Pfizer's Center of Excellence in Precision Medicine (CEMP) based in Santiago, Chile.

4.3.4. There are limited efforts to build professional and public knowledge about the role of precision medicine in health care

So far, limited systematic efforts have been undertaken to improve the knowledge and understanding of precision medicine and public health genomics amongst doctors, nurses and other health care professionals in Chile. Education is a critical issue if the aim is for genetic services to inform public health and preventive care, in addition to supporting diagnosis (Burke & Korngiebel, 2015). The provision of the genetics services (test or otherwise) can only yield benefits when the information is used to inform preventive or early intervention efforts. Such action requires knowledge among health professionals in primary and secondary care, as well as the public health policy community (Beskow, Khoury, Baker, & Thrasher, 2001; Burke & Korngiebel, 2015; Syurina, In den Bäumen, Feron, & Brand, 2012). In some OECD countries, including but not limited to the United Kingdom, capacity development for health professionals in the area of interpreting and translating genetic information to patients in a way that supports comprehension has been undertaken and is recommended (Relling & Evans, 2015).

Genetics literacy can be considered one aspect of health literacy, that is, individuals with high levels of health literacy have more capacity to comprehend genetic information. However, specific attention needs to be dedicated to educating the public to understand genetic information and critically, the implications of this information for their health, and the health of their family (Roberts, Dolinoy, & Tarini, 2014). There is a role for genetic counsellors in this process at an individual and family level. However, at a population level investment is also warranted for building genetic literacy more broadly (Burke & Korngiebel, 2015; Relling & Evans, 2015).

4.3.5. Regulation has not kept up with clinical advances in the clinical genetics field

Chile has established some key regulatory elements covering clinical genetic services, such as the requirement for clinical geneticists to be registered with the Superintendency of Health. However, important gaps are also apparent. Minimum standard and quality assurance requirements for clinical labs are generic, for example, with no specific requirements relating to genetics tests. This is a concerning deficiency because of the rapid development of genetic techniques, and the potentially devastating consequences of being given an incorrect analysis or a misleading interpretation. Furthermore, in Chile as elsewhere, an increasing number of commercial labs are being established and some offer direct-to-consumer testing, underlining the importance of robust regulation to protect the public. Currently commercial and academic labs in Chile send samples abroad for processing, so domestic capacity would need to be developed.

Chilean laws governing personal health data also do not adequately reflect the emerging landscape of genetic technologies. Current regulations allow sharing of individuals' health data only in very limited circumstances. This, however, may hinder growth of clinical genetics, because research and development in the speciality depends upon the analysis of patterns of genetic markers at population level and their correlation with disease.

The Personal Data Protection Project (PLDP) was registered under the instructions of the Chilean President in March 2017 (Bulletin No. 11144-07), and would update the current

data protection regulation (Law 19.628) and align it with OECD data protection standards. The PLDP includes specific provisions for the treatment of personal data related to health, biometric data and data related to the human biological profile, as well as for the use of personal data for various research purposes, and the treatment of personal data that shows location or history of movement.

The proposals set out under the PLDP likely need to be expanded, or added to under separate regulation, to ensure sufficient rigour when it comes to the handling and storage of genetic data. For example, the project does not cover the storage of data and their use in research or biobanks.

While the PLDP may be a good first step, further provisions may nonetheless be needed for the better protection of personal health data, including genetic data. A number of countries have introduced specific legislation covering the protection of personal health data (see (OECD, 2015; OECD, 2017). Such legislation could also cover the interoperability of health data, for example clinical records, prescribing, and eventually genomic records. Such data linkage could have the potential to increase the positive public health impact of genetic testing in Chile, both for individuals, and from a research and public policy perspective. Chile may wish to standardise the protocol for collection and use of genetic information sooner rather than later, and could look to the United Kingdom's consent form process as a possible model to follow (see Box 4.2).

A proposal has already been developed for the establishment of regulation of the use of samples and the sharing of data derived from biobanks in Chile. This regulation would cover the procedural and ethical aspects of the use and storage of human samples in biobanks for research purposes, and was drafted to reflect the perspectives of leading Chilean experts, as well as experts from countries such as Brazil and Spain.

Box 4.2. Consent form process for protecting and sharing personal genetic information in Genomics England

Assuring and gaining informed consent for the collection, use and storage of personal genetic information and where possible linkage of this information with other data sources is vital to the advancement of genomics. In Genomics England, arguably largest Whole Genome Sequencing project in the world (100 000 genomes project), the consent process involves the consent process involves giving information about participation in a routine medical appointment, potential participants are also asked to consider a range of factors in making their decision, including but not limited to: Linking participants' lifetime health records being linked to their genome sequence; Third parties accessing anonymised samples.

The participation of children under 16 is decided by their parents however, health professionals also work to help the children understand and seek their agreement to participate. When these children reach the age of 16, they will have an opportunity to make their own decision about continuing to remain involved, and consenting for their data to be shared.

It is also important to note that Genomics England provide a specific training course on obtaining informed consent for genetic testing for health professionals.

Source: Genomics England, 2018.

4.4. Current plans to develop precision medicine and genomics services

4.4.1. Chile is already giving serious thought to the future development of genetics and genomics at national level

The *Sociedad de Genética de Chile,* both a scientific society and a professional body, and the Ministry of Health jointly produced an analysis of Chile's needs in the field, publishing recommendations in December 2016. The joint review was comprehensive, identifying strengths and weaknesses in service provision, research, public education and awareness, regulation and international collaboration. Several of the findings and policy recommendations are reiterated in this Review.

Chile's goal to become a regional leader in the provision and research of clinical genetics services is ambitious. The collaboration between the government and genetics professionals, resulting in the 2016 report, is an important step in realising this goal. Likewise, public-private research collaborations (discussed below) are also indicators of a mature system.

However, translation of ambitions into policy remains partial. For example, there are currently no policies in place to promote the integration of genomics into routine clinical practice, even though this bottom-up activity must clearly be the foundation of any national roadmap. Similarly, there has not yet been any systematic effort to improve knowledge and understanding of genetics and genomics services amongst doctors, nurses and other health care professionals, nor the public. This limits the potential uptake and impact of new genetic technologies in the health system.

4.4.2. Countries where clinical genetics is more robustly embedded within the health system may offer an example for Chile to follow

The national approach to clinical genetics in the United Kingdom is based on genomics and precision medicine. The work and developments in genetics are all grounded firmly in the NHS and managed through Genomics England, which has been established as an entity to guide this work. Specifically, the approach involves conducting the 100 000 genomes project, which is described in further detail later in this chapter, establishing Genomic Medicine Centres and developing a Personalised Medicine Strategy for the NHS. Further, while the research and work is being trialled and conducted, a National Genomic Data Centre is being built to ensure all data is stored safely, and is available for research purposes in the future (Hill, 2016). Lack of budgeting and limited evidence of the cost-effectiveness or efficiency of genetic testing established.

There have been no studies of the historical evolution or estimated future evolution of health system spending in relation to clinical genetics and genomics services in Chile. There are also no mechanisms to contain growth in spending related to clinical genetics and genomics. While this is currently not a priority (given that so few services are publicly-funded), it might be an issue in the future, particularly considering the focus on genomics and preventive health care and public health. Experience from other countries shows that low-value care (such as unnecessary testing) can become an important issue.

In addition to cost containment, and the challenges of managing inefficiencies, and appraising costs against benefits, are critical steps in making decisions on funding and budgeting. Unfortunately, there is a significant lack of studies on the cost-effectiveness of genetics testing, particularly for newer technologies and for the use of genetic testing to inform preventive or public health care (Wideroff et al., 2009; Payne et al., 2018).

The Centers for Disease Control and Prevention in the United States have developed a model designed to evaluate the use of genomics applications, and a similar institutional actor may be needed to play a similar role in Chile. The Centers for Disease Control and Prevention in the United States developed a model designed to appraise genetic tests and technology for translation to clinical applications and public health. The Evaluation of Genomics in Practice and Prevention (EGAPP) initiative produces recommendations on the utility and validity of specific genetic tests, and with regards to preventive care, the US Preventive Services Taskforce took the recommendations from the EGAPP, and applied them to screening for colorectal cancers, breast cancers and haemochromatosis. It is worth noting the EGAPP model provided a framework for systematic evaluation of genetic tests that considers clinical efficacy, cost-effectiveness, and broader societal and public health benefits.

The Chilean Ministry of Health already has in place a system for systematic evaluation of the properties, effects, benefits, risks and costs of a health technology (ETESA for is acronym in Spanish: *Evaluación de TEcnologías SAnitarias*). With sufficient political will and appropriate guidance from both national and international experts, the same system could be implemented for genetic and genomic testing. Partnerships with research institutions could facilitate systematic validation of test results in the Chilean population, and public support could facilitate the development of evaluation and economic evaluation of genomic technologies in the national health care system. Resources will need to be directed not just to building genomic research and screening capacity, but also to the technical, practical and organisational challenges of bringing such tests to the Chilean population (Payne et al., 2018). It is important to note that newer techniques including but not limited to DNA chip and massive sequencing methodologies are being developed which could minimise costs, as this methodology allows multiple tests to be performed simultaneously (Drummond, Hill, & Barton, 2003). However, the overall scarcity of evidence on tangible health and societal outcomes from investing in genomics against the costs of investment, means that Chile has very little evidence to base investment decisions on.

4.4.3. Chile has an active research community in the field of genetics

Scientific research in Chile is principally funded by the *Comisión Nacional de Investigación Científica y Tecnológica* (CONICYT, hosted by the Ministry of Education and soon to be moved to the newly created Ministry of Technology) and the *Corporación de Fomento de la Producción* (CORFO, hosted by the Ministry of Economy). Both offer support to research teams for up to five years, via various calls that research teams respond to through open competition, for funds up to around USD 1 million.

These, and other funds, have allowed Chile to develop a substantial research base in clinical genetics and the basic science underlying it. The country, in fact, has more sequencers per capita than any other Latin American country, supported by a network of high performance computing capacity. One particularly promising development is *Chile Genomico* (see Box 4.3). This is a research platform that investigates population genetics. Its findings may help this and other programs in the identification of inherited risk-factors for disease, including diabetes, hypertension and several types of cancer in the Chilean population. The research uses biomarkers in clinical samples held in various biobanks (and has not, as yet, created a biobank of its own).

Box 4.3. ChileGenómico

ChileGenómico is a collaborative research network bringing together geneticists, sociologists, mathematicians and public health professionals. The project is managed by the University of Chile, and also has leadership from the Ministry of Health and support from the *Fondo de Fomento al Desarrollo Científico y Tecnológico* (FONDEF), as well as from the University of Tarapacá, and National Committee for Science and Technology (CONICYT). ChileGenómico's network of experts aims to study and build knowledge of the genome of the Chilean population, investigating different genetic biomarkers and documenting the extent of population genetic diversity.

More than 3000 people have participated, and researchers are developing a set of ancestry-informative markers. Currently, these genetic markers are being used to validate the predictive power of published genetic markers of risk for common diseases while considering the mixture of ancestries in Chileans. This information could be combined with social and environmental factors to inform public health and prevention strategies.

The rationale behind the project is that a greater understanding of the genetic profile of the Chilean population will increase the efficacy and targeting of preventive programs and health care.

Research collaboration with the private sector is also emerging. In particular, CORFO has recently established a Centre for Excellence in Precision Medicine with Pfizer Chile.

4.5. Accelerating the provision of clinical genetics and genomics services in a sustainable, equitable way in Chile

Chile starts from a strong position in seeking to develop its clinical genetics to become a regional and global leader. There are nevertheless substantial further steps that need to be taken to realise this ambition. First and foremost, a coherent and comprehensive national strategy should be agreed on to steer development of clinical genetics and genomic services over the coming years. One key component of this will be to agree on the right degree of regulation that underpins the analysis and – critically – sharing of individuals' genetic data. Another key component will be agreement on incrementally expanding the range of diagnostic genetic services covered by insurers; GES will need to keep pace with developments in the field of genomics, in particular where clear therapeutic benefit and value-for-money can be demonstrated. Ambitious goals to increase "genetic literacy" amongst both health professionals and the public should be also pursued. Alongside all this, it will be important to renew emphasis on the core public health activities of social, environmental and behavioural change, and not allow them to be overshadowed by newer genetic technologies.

4.5.1. A Ministerial working party should develop a national strategy for clinical genetics and genomic services in Chile

The development of precision medicine services in Chile should be underpinned by a national strategic plan, whose development should be directly overseen by the Minister of Health. Core tasks would include determining the expansion of genetic services to be included in GES; deepening collaboration between existing labs (public, private and academic) and rationalising the provision of key genetic tests across laboratories as

appropriate; ensuring that regulations (particularly around laboratory quality assurance, data sharing and consent) are fit for purpose; and, developing a programme of public and professional education around the role of genetic medicine. Most critically, a health system (especially one with relatively few resources) should only invest in new technology with a robust and detailed cost-effectiveness and budget-impact analysis, as well as business case. Chile's national strategic plan should ensure that this principle is adhered to.

A key element of the national plan should be to plan to concentrate selected genetic tests into specialist laboratories. At present, clinical genetics services in Chile are offered by a handful of public, private and university laboratories. These have arisen largely through individual initiatives, rather than a pre-planned approach. Such somewhat accidental arrangements are found in most health systems, but typically mean poor coordination and service gaps or duplication. Chile should bring order and coherence to the current landscape by agreeing a national strategy for clinical genetics services over the coming years.

Concentration and specialisation have the twin aim of improving quality and efficiency, and is increasingly pursued across OECD health systems in areas such as cancer care. As mentioned earlier, Chile is well supplied with sequencers. The working party that agrees such consolidation should involve all stakeholders (and clinicians and laboratory scientists in particular), but be led, and have Terms of Reference set, by the Ministry of Health. Given the importance of such a strategy, chairing by a Minister or Vice-Minister of Health would be appropriate; this would mirror the approach recently recommended in England.

Another key priority for the national strategy should be to identify and fund one laboratory to provide whole-genome sequencing. Currently Chile has limited capacity for clinical-grade WGS, meaning that samples are sent abroad for analysis. WGS is a core technology, so it seems that expertise and capacity in the technique need to be developed if Chile intends to become a regional leader in clinical genetics. The need for WGS arises relatively rarely, so a single national laboratory providing it should be sufficient. Other genetic tests that are indicated more often (such as panel testing for cancer susceptibility) would ideally be allocated to more than one laboratory, with different labs specialising in different services.

Additionally, all clinical genetics laboratories should be networked into a national virtual lab. Concentration of selected activities into selected laboratories does not imply fragmentation of services. On the contrary, rationalisation should be used as a lever to deepen collaboration between public, private and university research laboratories. In particular, a core task of Chile's national strategy should be the creation of a single, national virtual laboratory. The key activities of the virtual lab would include: providing advice to clinicians on appropriate tests in particular situations; ensuring rapid allocation of tests and samples to the appropriate specialist lab; the creation of national registers of the results of genetic analyses and linked phenotypic data; and planning a coordinated national research effort. Together, these activities should accelerate Chile's progress toward becoming a regional leader in both clinical genetics services and scientific research.

The Ministry of Health should also accelerate investment in telemedicine, as well as the development of interoperable electronic health records, in particular making effective linkages with the current broader development agenda around telemedicine. In parallel to the creation of a single, national virtual laboratory, other steps will need to be taken to

underpin a unified national genetics service. In particular, concentration of selected activities into fewer laboratories implies greater use of telemedicine to facilitate face-to-face communication between clinician, laboratory and patient. Telemedicine is developing rapidly in Chile (given the considerable geographic isolation of many communities), and benefits from a dedicated Division within the Ministry of Health. Clinical genetics should be a priority area for the further development of telemedicine in Chile, supported by national clinical frameworks and guidelines. Likewise, the need to share the results of genetic analyses and linked phenotypic data across Chile should be used as an impetus to drive development of interoperable electronic health records.

4.5.2. Appropriate regulation should underpin analysis and sharing of individuals' genetic data

Regulations specific to genetic data should be developed that permit sharing whilst protecting confidentiality. Genetic data is not the same as other types of personal health data. To approach a diagnosis, an individual's genetic (and phenotypic) data must be compared to the wider population, so that relevant variants linked to particular diseases can be found. Currently, Chile has strict regulations governing how personal health data can be shared. The current framework treats all personal health data equally, and is reported to be overly restrictive with regards to genetic data, risking progress in the field. Revised regulations that specifically relate to the sharing of genetic information would be welcome, therefore, to supplement the current regulatory framework. This would enable sharing of genetic data whilst protecting the privacy of identifiable personal data. As is already well understood in Chile, a red line is that individuals are not discriminated against (whether in terms of access to insurance, employment of other markets) because of their genetic profile. Patients should be involved in revising the regulatory framework that applies to genetic data.

Chile should build a national register of genetic variants, linked to phenotypes, to better understand inherited causes of disease. As a first step the registration platform for rare diseases, the Registry of Rare Diseases, which was presented in March 2018 but has yet to be enacted, should be linked with relevant genetic records and databases. As part of the unified national genetics service discussed earlier, and underpinned by revised regulations governing the sharing of genetic data, Chile should start to build a national register of genetic variants linked to phenotypes. This will need to be a dynamic register, continuously updated as individuals' phenotypes evolve and as the population's distribution of genetic variants extends. Linkage with *Chile Genómico* should be another priority, at the very least for research purposes. Informing the general public of the value of sharing genetic data, and the safeguards in place to protect against discrimination, will be vital.

Robust quality assurance should guarantee minimum standards across all laboratories undertaking genetic analysis. To ensure public confidence in a consistent standard of quality, robust quality assurance for clinical genetics laboratories and services should be developed. The precise approach should be agreed by all stakeholders in the Ministerial working party discussed earlier, and may involve peer-review or accreditation. Accreditation standards developed elsewhere are available to support this, such as those developed by the American College of Pathology. The College of American Pathologists holds a laboratory accreditation program, in collaboration with the American College of Molecular Genetics. This program outlines standards (and a checklist), that laboratories need to meet in a two-year period in order to be accredited to perform tests on human. Non-US laboratories can also be accredited with the Colleges. To-date the college has

accredited close to 8000 laboratories in 50 countries worldwide. Some academic laboratories in Chile (LGDM.PUC and CGG-UDD) are already participating in College of American Pathologist proficiency testing for genetics. This is a promising sign that such engagement could be broadened in Chile.

For Chile, this accreditation program may support the development of quality assurance processes, although investment in developing context-specific standards may be warranted (Grody & Richards, 2008). Rather than one-off assessment of minimum standards, however, it may be more effective to develop a programme of continuous quality improvement for labs and services, underpinned by regular audit cycles and other techniques, such as those developed by the Institute for Health Care Improvement.

4.5.3. The range of clinical genetic services covered by health insurers should be incrementally expanded

Incremental expansion of the range of clinical genetics services included in the GES is warranted, because the GES has not kept up with novel diagnostic technologies offered in other health systems. Furthermore, several conditions with an important genetic component are included in GES, but genetic tests that could speed up, or clarify, their diagnosis are not included. Clearly, expansion of GES needs to be sustainable and incremental, guided by cost-effectiveness and budget-impact analyses. Again, this is work that could be undertaken by the Ministerial working party described earlier.

An increasing body of research and international experience is available to support the task. It is recognised, for example, that whole genome sequencing (WGS) should be limited to rare or complex disorders whose diagnosis via non-genetic pathways would otherwise be lengthy. In more common disorders, more focussed analysis of the selected regions of the genome is more efficient in determining genetic antecedents. Likewise, population-wide sequencing is also poorly cost-efficient, with targeting to specific groups first stratified by phenotype, again being more efficient. Although such techniques (set out in Box 4) may capture the public imagination less that WGS, it is important that Chile should work to ensure equity, quality and sustainability of access to these "silver-level" technologies, and not invest inappropriately in "next generation sequencing".

Box 4.4. Going deep rather than wide: focused priorities in expanding the genetics component of GES

As has been alluded to across OECD countries, the development of genomics currently is quite focused and guided by strategic priorities for the health system overall. With the evolution of 'Next-Gen' sequencing methods, genomics has moved from sequencing being an arduous process that took considerable time, to rapid whole exome and whole genome sequencing being a possibility. However, with the breadth of possibilities in genomics there is a need to be focused in the priorities, for ethical and social reasons as well as economic ones. For instance, Next-Gen sequencing methods can assist with patients who may have symptoms within a disease family, but diagnosis of a specific disease has not been possible until genetic information is identified. These methods also help with identifying a susceptibility to certain cancers, e.g. BRCA (Scheuerle, 2017).

However, one of the challenges with these methods is that information can only be interpreted when compared with data from a broader population, and often that population is limited with respect to ethnic diversity, age and so forth. Despite the limited

diversity in these populations, there has been commercial testing and pharmaceuticals developed based on this information, which may have varying levels of effectiveness for individuals with different characteristics, and hence existing ethnic disparities in health outcomes are at risk of widening (Haga, 2010).

Therefore, Chile's commitment to genome sequencing and identifying ancestral history on a considerable population sample is a step towards ensuring that gene panel testing, or other genetics testing using Next-Gen methods will be more likely to reflect the true population characteristics.

In determining additional genetics tests to be included in GES, Chile again is starting from a good position. Professional and scientific associations have already drawn up a list of priority services to be added to GES. In terms of disease areas, the stated priorities with an important public health or preventive care component include breast, gastric, colorectal and prostate cancer. In terms of new techniques, priorities include MLPA, Sanger sequencing (which can analyse contiguous DNA sequences beyond 500 nucleotides), and molecular karyotype, which can identify Copy Number Variations.

The capacity of the Chilean health system to take action on significant genetic findings should be explicitly addressed. A key criterion in determining the expansion of GES's genetic component should be the actionability of abnormal results. A different – and more critical – aspect of actionability arises when a result becomes effectively unactionable because the health system in Chile is not configured to deliver an intervention that is known to offer benefit. For example, if BRCA1 and BRCA2 testing were to be introduced, GES's omission of prophylactic mastectomy for women who want it, renders BRCA testing effectively unactionable. Hence, the capacity of the wider system to take action on results needs to be explicitly addressed when considering expansion of the genetic component of GES.

4.5.4. Ambitious goals to increase "genetic literacy" amongst both professionals and the public should be pursued

Clinicians, including those working in primary care, should be offered training in when and how to refer patients for genetic analysis. Expansion of services will require workforce development, across both specialists (such as oncologists) and the primary care workforce. Properly training primary care clinicians in the potential of genetic analysis is critical, particularly if the objective is to improve preventive care and early diagnosis. This need not be highly technical, one of the most useful genetic "investigations", for example, is a thorough and well-documented family history. This can be easily performed in primary care practitioners, for example, and may reveal increased likelihood of cardiovascular disease, cancer or other important conditions. Equipped with this knowledge, personalised advice on prevention and early diagnosis can be offered. The United Kingdom offers a model here: 700 person-hours professional training in clinical genetics will be funded as part of a national strategy to increase genetic literacy.

The protocols and guidelines within GES should be updated to include a stronger focus on when a genetic component is likely, when and how to record a family history, and when and how to refer for further genetic analysis. From a preventive and public health angle, such updating of GES guidelines is particularly important for cancers or cardiovascular disease presenting at a young age. A particular priority, for example, is breast cancer where 10-20% of cases may have a hereditary component. GES guidelines should require, therefore, that a detailed family history should be taken in every new case,

so that early diagnosis or preventive care can be offered to family members at high risk. Similar considerations apply to gastric, colorectal and ovarian cancer. Guidelines that support the identification of hereditary cases of these cancers have been developed in other countries (such as the National Comprehensive Cancer Network guidelines of the United States, or the National Institute for Health and Care Excellence guidelines in the United Kingdom), and provide models for Chile to consider.

Developing genetic counselling services should be a priority for Chile. Interpreting genetic risk, considering this information alongside an individual's associated environmental risk, and explaining the combined risk and management options to patients is highly complex. As a result, a number of OECD health systems are investing in training more genetic counsellors to help patients make informed decisions with regards to prevention and treatment strategies. Chile, has recognised the importance of doing the same, and plans to establish genetic counselling services.

Educational initiatives for the general public should explain the role of genetic analysis, and the value of sharing individuals' genetic data. Initiatives to increase public understanding of clinical genetics will be just as important as initiatives directed toward professionals. Key objectives in increasing public understanding should be to explain role of genetics in disease aetiology and how that information can be used to improve disease prevention and treatment options, with a particular emphasis on the fact that pursuing a healthy lifestyle will always be necessary, irrespective of genetic risk. Encouraging data sharing, and addressing public concerns about genetic discrimination, should also be emphasised. The model of counselling and consent used at the point of genetic testing will be critical here. Again, the United Kingdom offers one approach to consider (see Box 5). There, consent is essentially permissive (allowing individuals' data to be used for research and quality improvement), but consent forms and linked educational resources are very detailed. Finally, public education should also address the emergence of commercial genetic testing. In some cases, this is of dubious scientific validity; in other cases, the lack of accompanying professional counselling risks creating anxiety or misunderstanding. As mentioned earlier, patient groups should be fully involved in developing a programme of public education.

Box 4.5. UK 100 000 Genomes project and United States All of Us initiative

A growing number of OECD countries have been large scale population level precision medicine initiatives. Canada, China, Estonia, France, and Korea have all been advancing precision medicine at a national level (OECD, 2017[2]). The United Kingdom and the United States also have very significant precision medicine initiatives, which are informing health policy and research in significant ways.

The United Kingdom established Genomics England within the National Health Service to deliver the 100 000 genomes project, which is focused on sequencing 100 000 genomes from approximately 70 000 patients and their families who live with rare diseases, as well as those with common cancers.

The aim of the project is to not only yield genetic information, it also involves linking this data with other health data at an individual level, including interviews with patients. Hence, the genetic information is combined with rich phenotype information. Further, within the project there are clinical interpretation partnerships where health professionals as well as geneticists work together to interpret all of the data. To enable further research

an anonymous version of all data is shared with researchers, to investigate potential clinical applications.

One of the main enablers, or features fundamental to the design and success of the 100 000 Genomes project is the design of the NHS itself, that is, there is an interoperable system in place where information from a variety of sources about an individual can be shared, and linked. Leaders of the project note that this is fundamental to its implementation and design, but a similar project in Chile would require significant investment in system structures to enable data linkage between clinical and genetic information, development diagnostic-level genomic services in private and public health care providers, and effective interaction between research and health care professionals and objective. If Chile was to implement a national initiative of genomic medicine new and adapted government-industry structures would be need to reach these goals.

The United States' All of Us initiative (formerly know as the Precision Medicine Initative) is run by the National Institute of Health and began in 2015 with a significant investment of USD 215 million, and had the aim of collecting genetic and environmental information for one million people (OECD, 2017[2]). The initiative is designed to collect data over a decade-long period drawing from sequencing, Electronic Medical Records (EMRs), personally reported information, personally reported information, and digital health technologies (Ginsburg and Phillips, 2018[7]). Participation is open to all, and participants will have access to information gathered about them.

Although the health system in the United States is organised very differently than in the United Kingdom, the initiative was also launched because of changing possibilities in the field of personalised medicine, as well as health care system design conditions. Most notably, part of the motivation behind the launch of All of Us was the changing cost of DNA sequencing, alongside the growth of other data sources (e.g. EMRs) (Ginsburg and Phillips, 2018[7]).

4.5.5. Core public health goals of bringing about social, environmental and behavioural change should not be overshadowed by new genetic technologies

A major challenge for Chile and other countries is the translation of the increasing amount of new knowledge produced by genomic technologies into public health policies and whether it will lead to improved population health. For a proper understanding of an individual's or community's risk of disease, genetic information must be combined with the information provided by behavioural, social and environmental risk factors to estimate an overall level of disease risk.

Decisions to invest in new genomic technologies will need to be carefully balanced against the need for investment in other parts of the health system. Chile is a relatively under-resourced health system, compared to OECD peers, in terms of workforce numbers, hospital bed density and the supply of key technologies such as CT and MRI scanners. Therefore, investment decision in these technologies should be based on strong evidence of effectiveness and cost-effectiveness. Turning to public health specifically, the core activities of risk-factor surveillance, screening, regulation, persuasion, education and so on will never diminish in importance, despite the growing profile of public health genomics. Chile should balance overall investment in genetic technologies with recommendations for strengthening traditional public health made in the other chapters of this report.

4.6. Conclusion

The potential for the role of precision medicine in supporting the public health and preventive care efforts in Chile has been explored in this chapter. The current work and plans for the growth of precision medicine in Chile is encouraging, and the work of academic, clinical and other research labs are critical not only for the Chilean population, but hold potential to valuably contribute to broader research in this field. However, there remains particular system challenges for Chile in broadening public health genomics and informing public health and preventive care.

The from this chapter recommendations focus on addressing these challenges. Specifically, the clinical genetics workforce is lacking a necessary group of expertise, that is, genetics counsellors. Further, the proportion of genetics laboratories in Chile is small, and they are also not widely located or linked throughout the country. In addition, most of the genetics testing is using older methods, and these are often not funded within the public or private health insurance system in Chile. Addressing access (financial and geographical) inequalities and establishing quality methods and regulation for laboratories is necessary. Regulation is also required for health professionals and precision medicine specialists on data sharing, confidentiality, safety, linkage and management. Patient consent procedures need to be standard, particularly if genomics work is occurring across the country, and health professionals and genetic workers need to be educated in these procedures. Further, consideration to investing in genetics literacy and the information dissemination process of the potential and value of genomics is warranted, as it is only when this process is successful that clinical applications and public health advancements through genomics can occur. Finally, and critically, to take maximum advantage of the potential of public health genomics Chile should look to establish a comprehensive governance framework, addressing issues such as quality control, regulation, privacy, data management and research. With sufficient commitment – from the Ministry of Health in Chile as well as from genetics specialists –expansion and continued growth of precision medicine could make Chile a regional leader in this area, with the potential to contribute to tackling some of the most complex public health challenges of our times.

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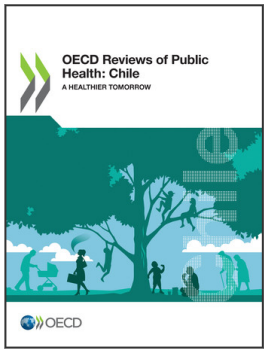

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