3 Public health genomics in Korea

In Korea, genomic medicine is a fast-growing and popular field: genomic research, genetic testing and precision medicine, and direct-to-consumer genetic testing, are significant areas of policy attention, while in terms of genomic research, Korea has one of the biggest biobanks in the world. Genetic testing is widespread and increasing, both for hereditary (mostly infant) diseases, and following cancer diagnoses to personalise treatment. A regulatory framework has been developed for these tests, but quality assurance of private testing laboratories and training for health professionals are less well-developed and, most importantly, health coverage does not appear to be keeping pace with demand from patients and clinicians, and the cost-effectiveness of widespread use of genetic testing to personalise treatment (in particular cancer) does not appear to have been established. The area which generates the most concern when it comes to genomic medicine in Korea is the booming field of direct-to-consumer tests genetic tests.

Introduction

In Korea, genomics is an exploding field: genomic research, large-scale genome genetic testing, genomic screening and diagnostic tests, precision medicine, and direct-to-consumer genomic testing, are significant areas of policy attention. This expanding domain could bring significant gains in Korea, from a deeper understanding of the population's genomic profile and disease risk, to earlier disease detection, and more effective treatment. There are, however, risks associated with the field of genomics, for example around the effective regulation of sensitive genetic information, ensuring equal access to cutting edge therapies, or ensuring that the use of genomics in health care is driven by the evidence-base, rather than potentially costly consumer or provider demand. This chapter will explore some of these issues, but this chapter will primarily take a public health focus, and address the extent to which genomics can be leveraged to improve population health and preventive care. The chapter will follow the definitions set out in Box 3.1; in this chapter the term 'precision medicine' is used to refer to the different applications of genomics (e.g. genetic testing or genome sequencing, precision or stratified medicine, or genomic research) in the health care and research field.

This chapter describes and assesses, in turn, the state of genomic research in Korea, the use of clinical genomics in Korea including genomic screening and precision medicine, and the field of direct-to-consumer genetic and genomic testing. Each section explores some of the strengths and shortcomings of the particular area of genomic use in Korea, with a focus on the implications for public health policy. A final section makes a series of recommendations for ways in which Korea could strengthen the use of genomics, with the objective of maximising the positive impact on population health.

3.1. Precision medicine and public health genomics

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

3.1.1. Precision medicine and public health genomics

Over the last two decades, and particularly with the sequencing of the human genome and advances in informatics and a range of technologies, new possibilities have opened-up in the field of medicine allowing an increasingly precise consideration of 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[1]). 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[2]). Public Health Genomics has been understood as the integration of genomic-based knowledge into public health policy and population health (Boccia et al., 2009[3]; Bellagio Statement, 2005[4]; Burke et al., 2006[5]). 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 3.1).

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 (OECD, 2017[6]): "[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" (OECD, 2017[6]; Innovate UK, 2016[7]).

Box 3.1. 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[8]; OECD, 2017[6]; Innovate UK, 2016[7]). 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[9]). **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 scrutinises 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[8]).

'**Sequencing'**, which is also referred to as **next-generation sequencing (NGS), parallel or high-speed sequencing** refers to a number of different modern 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[8]; Doble et al., 2017[9]; OECD, 2017[6]).

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[9]; OECD, 2017[6]). 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.

Sources: Phillips, K. et al. (2014[8]), "Genomic sequencing: assessing the health care system, policy, and big-data implications.", *Health affairs (Project Hope)*, Vol. 33/7, pp. 1246-53, http://dx.doi.org/10.1377/hlthaff.2014.0020; OECD (2017[6]), *New Health Technologies: Managing Access, Value and Sustainability*, OECD Publishing, Paris, https://dx.doi.org/10.1787/9789264266438-en; Innovate UK (2016[7]), *Mapping the UK Precision Medicine Landscape*, assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/853560/Precision_Medicines_Booklet_Final_Web_002_.pdf; Doble, B. et al. (2017[9]), *Prioritising the application of genomic medicine*, http://dx.doi.org/10.1038/s41525-017-0037-0.

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[10]). 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[11]) – these new and rapid developments nonetheless pose new challenge for health policy makers, many of which this chapter seeks to explore.

3.1.2. Precision medicine may advance preventive health care and public health more broadly

Precision medicine can be used as a powerful diagnostic tool, to test for congenital abnormalities, inherited conditions, and diagnose other conditions.

For children born with a major congenital abnormality, around one third will have a genetic component such as Trisomy 21 (Down's Syndrome), and identification of the underlying genetic cause is important to understand prognosis, guide treatment decisions, and support parents when considering having additional children. 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).

The development of genomic medicine, and in particular NGS, can also bring new perspectives on rare diseases, both at an individual level and at a population level (Wordsworth et al., 2018[12]). For example, Wilson's disease, which is caused by a gene mutation (of the ATP7B gene) results in copper accumulation in the liver, and can lead to hepatic, neurological or psychiatric symptoms (Jang et al., 2017[13]). A DNA-based screening approach is not only an effective diagnostic tool for Wilson's disease, but can also glean population-level insights, for example the finding that the carrier frequency of Wilson's disease in the Korean population is higher than previously thought (Jang et al., 2017[13]).

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 could allow screening programs to offer more aggressive screening and surveillance regimen to these groups (Pashayan et al., 2013). Or, genetic information could be combined with other forms of health information – for example traditional medical testing – as well as information about environmental and behavioural risks and context.

For some time there has been a general expectation that increased precision could offset other unnecessary tests and yield cost savings, and some evidence is beginning to emerge for cost-effective genetic screening interventions. For example, there is some evidence of the cost-effectiveness of using NGS panels for screening for Lynch syndrome, or screening for women at risk of hereditary breast cancer (Doble et al., 2017[9]). In general though there is still limited evidence for the cost-effective whole exome sequencing (WES) and whole genome sequencing (WGS) (Schwarze et al., 2018[14]).

However, at this point, common diseases including, but not limited to, cancers and many cardiovascular diseases, have been found to be more genetically complex than was first anticipated. To take an example, Ischaemic Heart Disease (IHD) has a hereditary component, but this information is less predictive than a range of traditional tests, including blood pressure, blood cholesterol or body mass index at determining IHD disease risk (Howson et al., 2017[15]; Khoury, Iademarco and Riley, 2016[16]). A 2018 systematic literature review found that evidence of the cost-effectiveness widespread use of WES and WGS is very limited (Schwarze et al., 2018[14]). To take another example, screening for some cancers can be informed by genetic screening, for example screening for hereditary mutations on the BRCA 1 and BRCA 2 genes, which are known to significantly increase cancer risks, especially for breast and ovarian cancer. Such screening can lead to increased screening (for example more frequent self-checks or mammography), preventive medication or even surgical intervention, which can be effective at significantly reducing risks from cancers arising from this specific mutation (see Box 3.3).

3.2. Genomic research and gene mapping in Korea

3.2.1. The National Biobank of Korea and gene mapping project

Korea has one of the biggest biobanks in the world, the National Biobank of Korea and biobank network (Lee et al., 2012[17]; Cho et al., 2012[18]). Established in 2008, the biobank at the National Institute of Health, depends on a sophisticated network of 17 biobanks spread across Korea. Each regional biobank can secure and store the biospecimens, and inputs standardised samples and clinical information into the Human Biobank Information Systems (HuBIS) which is run by the National Biobank of Korea. Including specimens held in regional biobanks, the Korea Biobank Network (KBN) holds human biospecimens from more than 820 000 participants, from the general population and from diseased populations (around 50% of specimens are held at the National Biobank of Korea in Osong).

The information held includes human biospecimens – blood, body fluids, tissues, serum, plasma, and DNA – but also personal information related to health records, life style, family history and genetic information. The information and biospecimens have been collected through the Korean Genome Epidemiology Study (KoGES), Korea National Health and Nutritional Examination Survey, and other research project under the Korean National Institute of Health (Cho et al., 2012[18]). Resource information of human biospecimens and their related data have been shared through the web-based Korea Biobank Network (KBN) system. The biospecimens and related data stored in the biobanks can be used by researchers whose applications are approved by the Distribution Review Board. As of end-2017 an estimated 894 papers had been published using data and specimens from the biobank (KNIH, 2018[19]).

The National Biobank of Korea complies with the *Korean Bioethics and Safety Act* and the *Act on the Acquisition, Management, and Utilization of Bio-Resources for Research*; clear guidelines for sample integrity, including DNA, are established, and quality tests are encouraged for the regional biobanks (see (Lee et al., 2012[17]). All data is anonymised and shared securely, but in the case of disease-related biospecimens, the limited information from the individual's Electronic Medical Record (EMR) is periodically transferred to the Human Biobank Information Systems.

The first Korean individual genome sequence (SJK) and analysis results was published in 2009 (Ahn et al., 2009[20]). As part of the National Biobank of Korea, a number of large-scale genomic projects have been undertaken, including the Korean Genome Analysis Project (KoGAP) and the Korean Reference Genome (KRG). This effort, undertaken by the Center for Genome Science of the National Institute of Health (NIH) and the Centers for Disease Control and prevention (CDC), published whole genome sequencing for 622 Koreans by 2012, and had identified many newly detected Korean genetic variants. Another large scale genomic study, Korea Association Resource (KARE) and many researches utilised the biospecimens

secured through Korea Genome Epidemiology Study (KoGES) and Korea Biobank Project (KBP) (Cho et al., 2012[18]).

3.2.2. Using the Korean Biobank, Korean Genome Project and other genomic initiatives to strengthen population health knowledge

The biobank is already generating significant research, some of which is clearly relevant to deepening understanding of public health risks in Korea. Since the establishment of the biobank research has looked at the relationships between genes and diseases, behaviour and environmental risks. KARE/KoGAP aims to identify genetic and environmental risk factors leading to the development of five common life-style-related diseases (i.e. obesity, diabetes, hypertension, osteoporosis, and metabolic syndrome) in a large number of Korean populations. (Lee et al., 2012[17]). KARE used 8 842 Korean DNA samples to identify genomes related to hypertension, the waist/hip ratio, and bone mineral density (Cho et al., 2012[18]; Kim et al., 2011[21]); another study highlighted previously unknown biological pathways for nine metabolic traits by combining the Korean genome information from the KARE project with data in BioBank Japan (Kim et al., 2011[21]). The biobank is also informing research around personalised medicine.

The Korean genome and epidemiology study (KoGES) is an example of the commitment of the Korean Government to harnessing the potential of precision medicine for public health. KoGES is funded by the Korean Government, delivered through the National Institute of Health (NIH), Centers for Disease Control and Prevention and the Ministry of Health and Welfare. It integrates six prospective cohort studies categorised into population-based and gene-environment model studies. The study aims to address the genetic and environmental aetiology of a number of common (chronic) diseases, such as type 2 diabetes, cardiovascular disease and cancer, as well as risk factors including hypertension, obesity and metabolic syndrome (Kim, Han and KoGES group, 2017[22]).

KoGES has already established a range of findings with potential relevance to public health, and public health policy, some of them drawing on information on genetic variants (Kim, Han and KoGES group, 2017[22]):

- Identification in genetic variants in Asian Korean populations associated with type 2 diabetes, blood pressure, waist-hip-ratio, bone mineral density and serum lipid level;
- Identification of protective factors for metabolic syndrome, including an increased baseline serum adiponectin level, and for diabetes (high plasma concentration of isoflavones in women, suggesting a beneficial effect of soy-based food intake);
- Demonstration that haemoglobin A1c (HbA1c) cut-off values of 5.9% and ≥ 5.6% can be effectively used to identify undiagnosed type 2 diabetesT2DM and an increased risk for disease incidence, respectively.

However, the translation of these findings into policy making and effective public health strategies seems under-developed, and it is not clear whether the Ministry of Health and Welfare are well-briefed on relevant research from the biobank.

3.2.3. Linkage of genetic information and other health system data is critical

For genomic research, preventive interventions, and clinical application, precision medicine, linkage of genomic data with other health system data, and/or the inclusion of individual's genomic information in personal medical records as it becomes available, would contribute to a far richer information source and potentially greater relevance for public health genomics. At present, the Korean Biobank does not provide linkage of genomic data with other secondary data such as health or medical information.

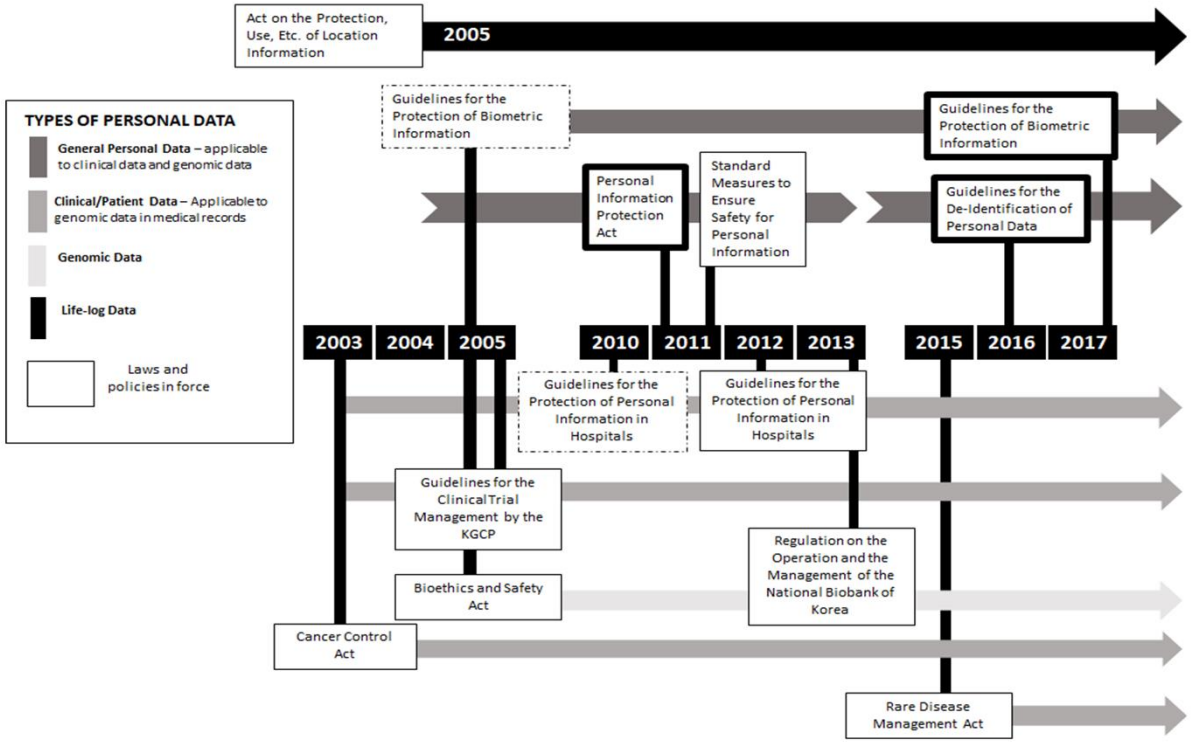
Korea has been identified as having one of the strongest health information systems in the OECD. In Korea around 80% of data sets covering at least 80% of the population, more than 90% of datasets sharing the same unique patient ID, and more than 70% of datasets regularly linked for research, statistics and/or

monitoring (OECD, 2015[23]). Korea's health data governance legislation allows relatively open sharing of (identifiable) personal health data amongst public authorities, but personal health data from the Health Information Regulation Agency (HIRA) cannot be shared outside of the public sector, including with academic institutions. De-identified data can be lawfully shared with researchers working in the public, academic and non-profit sectors.

Korea has an extensive legislative infrastructure for health data, although different sources of data are collected under different legislation, including for example a Cancer Management Act and a Genetic Management Act. Many of these individual Acts have clauses related to data sharing, while the Statistics Act covers data holdings (OECD, 2015[23]). Significant debates on information security and linkage are also ongoing, both in terms of data use for research and for clinical practice. The Korean government has made utility of its health data infrastructure a priority, including introduction of new guidelines on the protection of bio-information as recently as 2017 (see Figure 3.1) (Kim, Kim and Joly, 2018[24]).

Figure 3.1. Data Protection and Regulation in Korea

Timeline of key Legislation around health data protection in Korea



Source: Author's elaboration based on Kim, Kim and Joly (2018[24]), "South Korea: in the midst of a privacy reform centered on data sharing", *Human genetics,* Vol. 137/8, pp. 627-635, http://dx.doi.org/10.1007/s00439-018-1920-1.

At present, information from Korea's biobank cannot be linked to HIRA or NIH data systems, even in an anonymised way. If it were possible to accelerate these connections, there is potential for this data to be a valuable source of research and a first step in establishing a big data system that includes genetic information.

3.3. The use of precision medicine for preventive interventions and public health

Genetic testing is widespread and increasing in Korea, both for hereditary (mostly infant) diseases, and following cancer diagnoses to personalise treatment. A regulatory framework has been developed for these tests, but quality assurance of private testing laboratories and training for health professionals are less well-developed. Most importantly, health coverage does not appear to be keeping pace with demand from patients and clinicians, and the cost-effectiveness of widespread use of genetic testing to personalise treatment (in particular cancer) does not appear to have been established.

3.3.1. Use of genomics in Korea

The Korean Government's genomics policy is overseen by the Division of Bioethics Policy, in the Bureau of Public Health Policy, in the Office for Healthcare Policy in the Ministry of Health and Welfare (see Box 3.2). The primary legislation for the use of genomics in health care is the Bioethics and Safety Act (Republic of Korea, 2014[25]), which was amended extensively in 2012, and then further amended in 2015 to introduce further regulation on genetic treatment research. A National Bioethics Committee informed the revision of the law (Box 3.2).

Box 3.2. Korea's Law on Bioethics and Safety

The National Bioethics Committee in Korea informs the Law on genetics, which appears to be relatively comprehensive. For example, the Law bans tests with low scientific evidence, and places restrictions on embryonic/in vitro testing (60 embryonic tests are currently allowed).

Table 3.1. Ammendments to Korea's Bioethics and Safety Act

Bioethics and Safety Act – original	Bioethics and Safety Act – amendment 29 December 2015
Article 50 No genetic testing institution, other than a medical institution, shall conduct a genetic test in connection with the prevention, diagnosis, or treatment of a disease: Provided, That the foregoing shall not apply to a genetic test conducted at the request of a medical institution.	Article 50 No genetic testing institution, other than a medical institution, shall conduct a genetic test in connection with the prevention, diagnosis, or treatment of a disease unless it falls under the following cases: 1. Where it is requested by a medical institution; 2. Where it conducts a genetic test related to the prevention of a disease, the necessity* of which is recognized by the Minister of Health and Welfare. If genetic testing is conducted by a genetic testing institution, other than a medical institution, the limitations and scientific basis of the test results should be specified in the result sheet and fully explained to the test subjects. *Regulation on genetic test items that can be conducted directly by a genetic testing institution, other than a medical institution [Enactment Date June 20, 2016] [Ministry of Health and Welfare Notice No.2016-97].
	Bioethics and Safety Act – further amendment SPRING 2019 Complete with further info, e.g. coverage of dementia testing

Source: Republic of Korea (2014[25]), *Statutes of the Republic of Korea: Bioethics and Safety Act,* https://elaw.klri.re.kr/eng_mobile/viewer.do?hseq=33442&type=part&key=36.

With regards to genetic testing in the health system, with the use of certain clinical tests restricted. For example, testing for BRCA 1/2 can only be undertaken if breast cancer is detected or the individual has a strong family history of breast cancer. In general, genetic testing is usually used for hereditary diseases, and cancer diagnoses, in order to refine the cancer treatment approach. Overall the volume of genetic tests has been increasing in Korea, but there has not been a comprehensive study assessing this expansion, and concrete, quantitative evidence is hard to find. Current permitted tests are listed in Table 3.2.

Table 3.2. Current permitted NGS Genetic Panel Testing in Korea

Disease area and gene permitted for testing in Korea

Disease	Mandatory gene
Hereditary retinitis pigmentosa	PRPF31, RHO, RP1, RP2, USH2A, PRPH2, RPGR
Hereditary hearing loss	GJB2, POU3F4, SLC26A4, TECTA
Charcoal maritus disease	GJB1, MFN2, MPZ, PMP22
Other hereditary diseases excluding the three mentioned above	None
Solid Cancer	HER2,EGFR,ALK,KRAS,NRAS,BRAF, BRCA1,BRCA2, KIT,PDGFRA,IDH1IDH2, MYC(C-myc),N-myc(MYCN)
Plasma cell tumour	NRAS, KRAS, TP53
Acute myeloid leukaemia	CEBPA, FLT3, JAK2, KIT, NPM1, RUNX1, TP53, IDH1, IDH2
Acute lymphocytic leukaemia	TP53, RB1, JAK2, NRAS, IKZF1
Myelodysplastic syndrome, myeloproliferative tumours	ASXL1, CALR, CSF3R, DNMT3A, JAK2, MPL, RUNX1, SETBP1, SF3B1, SRSF2, TET2
Malignant lymphoma	MYD88, BRAF, TP53

Source: Information supplied to the authors by the Korean Government, based on Ministry of Health and Welfare Notice No.2017-15.

Most genetic tests are not covered by Korea's National Health Insurance Service. Some genetic tests, for example for cancer, are covered by private insurance; around 68% of the population in Korea are covered by supplementary/complementary health insurance (OECD, 2017[26]). However, many tests are paid (at least partly) out-of-pocket. Next Generation Sequencing panel testing is sorted into two types, Level I and Level II, with different costs; Level I and Level II tests incur a 50% co-payment for the patient, with Level II tests having a higher price (see Table 3.3). For example, the co-payment rate for solid cancer is 50% in the case of progress, metastatic and recurrent cancers, but the co-payment rate rises 90% for some other cancer patients. Depending on the patient's condition, different co-payment rates apply to National Health Insurance rates. There are also some limits on the number of genetic tests that can be undertaken, so that the same individual cannot repeatedly request testing (either different or the same), for example one genetic test for hereditary diseases, and one genetic test for non-hereditary diseases. One additional genetic test is authorised in the case of recurrence and treatment failure (information reported to the OECD by the Korean Authorities).

Table 3.3. NGS Testing levels and frequency permitted

Genetic tests included in different reimbursement categories

	Hereditary	Non-hereditary
Level I	The number of genes is 2 to 30, or the gene length is 150 kb or less	The number of genes is 5 to 50 or the gene length is 150 kb or less
Level II	If the gene length exceeds 150kb or more than 31 genes, it is recognized only for hereditary retinitis pigmentosa, hereditary hearing loss, and Charcot maritus disease.	The number of genes is over 51 or the gene length is over 150 kb
Frequency	1 time per disease	1 time at diagnosis However, in case of recurrence and treatment failure only one additional authorisation

Source: Information supplied to the OECD based on Korea's National Health Insurance Service coverage.

There do not appear to be any guidelines in place – either for physicians or consumers – regarding the prescribing of genetic tests. This situation has the risk of creating incentives for hospitals to prescribe genetic tests in order to increase out-of-pocket payments, with little protection for patients who may not be in a position to assess the necessity of such a test. If genetic testing is to become a core part of the Korean medical landscape the government may wish to look for ways to provide coverage for tests that are evidence-based and with demonstrated clinical utility.

South Korea's Bioethics and Biosafety Act specifies that only medical institutions are permitted to undertake genetic testing connected with prevention, diagnosis or treatment, but an important exception exists if medical testing is requested by a medical institution, which allows for private companies to undertake processing of genetic test (Fukuda and Takada, 2018[27]). Indeed, in reality, much of the processing of genetic tests is undertaken by private laboratories, of which there are around 3-4 in Korea. Testing is prescribed by a doctor, and then run by private companies, who return the results to the doctors.

At present, there are no explicit or specialised quality checks in Korea around genetic tests. Genetic laboratories receive annual quality control management and accreditation from the Korea Institute of Genetic Test Evaluation (KIFTE). Currently, genetic tests are regulated as pharmaceuticals (manufactured reagents), and one NGS genetic testing panel is approved as a medical device.

The development of further regulations and/or quality check systems could be desirable. The development of further regulation around the use of genetic tests appears to be under consideration; Korea may wish to look to other OECD countries who have introduced certification and/or regulation systems for precision medicine. However, it is worth stressing that across OECD countries (and beyond) genetic testing is a relatively emergent area; in some instances technology has out-paced regulatory frameworks, or will soon out-pace newly established provisions (Table 3.4).

Table 3.4. Regulation around the provision of genetic testing in select OECD countries, 2018

Requirements for the provision of genetic testing in OECD countries

Country	Provision of genetic testing		
	Involvement of health professionals	Genetic counselling	Informed consent
Austria	✓	✓	✓
Belgium			
Canada			
France	✓	✓	✓
Germany	✓	✓	✓
Japan			
Portugal	✓	✓	✓
South Korea	✓		✓
Switzerland	✓	✓	✓
United Kingdom			✓
United States*	No federal legislation but covered in state law		No federal legislation but covered in state law

Source: Adapted from Fukuda, R. and F. Takada (2018[27]), "Legal regulations on health-related direct-to-consumer genetic testing in 11 countries", Kitasato Med J, Vol. 48, pp. 52-59, http://mlib.kitasato-u.ac.jp/homepage/ktms/kaishi/pdf/KMJ48-1/KMJ48-1p52-59.pdf.

3.3.2. The clinical genetics workforce in Korea genetic literacy amongst physicians

Overall, Korea has lower numbers of health professionals than the OECD average, and shortages of health professionals are a preoccupation for the Ministry of Health and Welfare. For example, in 2017 Korea had 2.2 physicians per 1 000 population compared to the OECD average of 3.4, and 5.9 nurses per 1 000 population compared to the OECD average of 9.0 (OECD, 2017[26]). Numbers of health professionals are

rising faster than average OECD-wide, but numbers of medical graduates remain well below the OECD average.

There is no clinical geneticist specialisation in Korea. Some specialisations have components of genetic training. Some graduate schools have genetics programmes, but they are not licenced by the government. There are 10-20 nurses who work on genetic medicine across the country. There are 36 genetic counsellors in practice in Korea, and 27 in training.

At present it is not possible to identify the number of graduate schools which have genetics programmes, the extent of 'genetic graining' in basic medical training or the options for genetics or precision medicine training in continuing professional development.

3.3.3. Using precision medicine for public health interventions

The Korean Government has clearly been making public health genomics a priority, and has been investing in research to try to operationalise genetic insights for public health. However, the government's focus appears to be the development of new treatments rather than preventive interventions.

For example, in 2017 the Korean Government invested KRW 63.1 billion (roughly USD 55.7 million) in developing precision medicine in a project led by Korea University to run until 2021 (Korea Biomedical Review, 2017[28]). The focus of this work is on developing personalised cancer treatments, starting with the analysis of the genetic information of 10 000 cancer patients. Related trials will also try to improve access to new forms of therapies, expanding indications of already-approved drugs.

However, despite investment in elaboration of some regulatory provisions, and investment in research activities, there seem to be clear translation strategy to integrate the findings of the existing research into effective precision medicine or public health policies.

3.4. The use of direct-to-consumer (DTC) testing

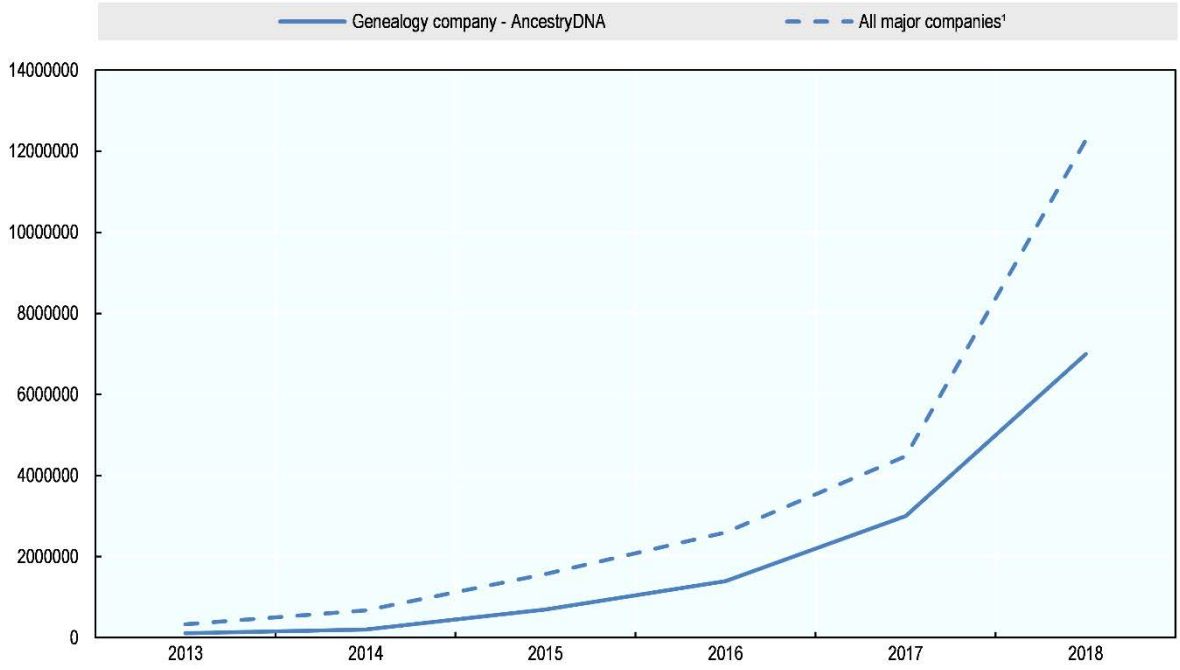
The area which generates the most concern when it comes to genomic medicine in Korea is the booming field of direct-to-consumer (DTC) genetic tests. At present, Korea allows a relatively limited number of DTC genetic tests, which give information such as genetic traits linked to blood pressure, cholesterol, skin elasticity, or hair loss. Cosmetic information for example on skin health or type. In early 2019 the Government agreed to explore the introduction of a further suite of DTC genetic tests for 13 diseases, such as coronary artery disease, hypertension, type-2 diabetes, stroke and a number of cancers. This section explores the current evidence base for the impact of DTC genetic tests on consumers' health behaviour, their effectiveness as tools to promote good health and prevent disease, and the potential risks to the population and to the health system associated with expanding the DTC genetic test market.

3.4.1. DTC genetic testing availability and regulation

Direct-to-consumer (DTC) testing allows people to access information about their genetic makeup without passing through a medical professional. DTC can make available health-related and non-health-related genetic information, for example vulnerability to certain diseases, or information on ancestry. In the past several years DTC genetic tests have more and more available in many OECD countries, oftentimes with regulation struggling to keep up with shifting supply, and indeed consumer interest and demand (see Figure 3.2). While the rate of testing by consumer genetic companies appears to have increased in Korea in recent years, official data tracking this trend is not available.

Figure 3.2. Rate of testing by consumer genetics companies in the United States 2013-2018

Total number of people tested, in millions



[1] Genealogy services operating in the United States

Source: Data based on MIT Technology Review (2018[29]), 2017 was the year consumer DNA testing blew up - MIT Technology Review, https://www.technologyreview.com/s/610233/2017-was-the-year-consumer-dna-testing-blew-up/ (accessed on 18 April 2019).

DTC tests are advertised as able to offer benefits ranging from satisfying curiosity in ancestry or heritage, to improving individual's understanding of their health, and improving health-promoting behaviours. The suggested benefits of greater access to DTC genetic tests include changing consumer behaviour, for example seeking to improve diet if shown to have an elevated genetic risk of obesity or high cholesterol. Genetic testing showing elevated disease risk could also lead to more targeted preventive actions, for example more frequent cholesterol testing, or more frequent mammography. A recent systematic review and meta-analysis of health behaviour change following a DTC genetic test showed that on average 23% of the included studies participants reported a positive lifestyle change after undertaking the test – including 12% reporting improved dietary and exercise practices and 19% quitting smoking (Stewart et al., 2018[30]).

Some genetic tests, including those which in some countries are now available as DTC tests, have led to preventive operations, for example preventive mastectomies for individuals with BRCA1/2 gene (see Box 3.3).

Box 3.3. Genetic testing for BRCA 1/2

Breast cancers due to mutations in the BRCA 1 and 2 genes represent one of the best illustration of the health benefits that genomic medicine could bring through targeted screening and prevention. BRCA 1 and BRCA 2 are two genes producing tumour suppressing proteins; mutations in these genes can lead to an elevated life-time risk and early onset of breast and ovarian cancers. It is estimated that 69-72% of women with a harmful BRCA 1 or 2 mutation will develop breast cancer before the age of 80, compared to 12% of women in the general population; an estimated 17-44% of women with a harmful mutation will develop ovarian cancer by the age of 80, compared to 1.3% of women in the general population (Kuchenbaecker et al., 2017[31]; Howlader et al., 2017[32]).

Many OECD countries, including Korea, offer BRCA gene testing under certain circumstances, for example following a diagnosis of breast cancer especially at a young age, family history of breast or ovarian cancer, or ethnic risk factors (notably the Ashkenazi Jewish ethnicity has a known vulnerability) (Walsh et al., 2017[33]). Testing can help tailor treatment if cancer has already developed, and can help women take certain steps to manage their risk of developing cancer in the event of a positive diagnosis, for example increased screening, preventative medication, or even risk-reducing surgery.

Some countries, and some DTC genetic testing companies, allow testing for BRCA mutations outside of medical establishments. This is not currently the case in Korea. BRCA is perhaps one of the best known genetic tests, in part due to the good understanding of the related risks, but also since American actress Angelina Jolie publicly discussed her own experience as a BRCA carrier, and the preventive surgery she underwent as a consequence (Liede et al., 2018[34]; Evans et al., 2014[35]). Consumer interest in the test is understandable, and appears to have had an impact in Korea also, with a rise in BRCA testing rate (Lee et al., 2017[36]).

However, DTC genetic testing for BRCA mutations come with some risks. DTC genetic tests can be inaccurate. Schleit et al. (2019[37]) detail the experience of one woman with a family history of breast cancer, for whom a DTC tested negative for BRCA markers, but for whom a clinical molecular genetic test showed she was a mutation carrier. DTCs often cover a narrow range of the known BRCA1/2 mutation, and can be based on a narrow ethnic sample of genetic data (Breast Cancer Action, 2018[38]; Schleit, Naylor and Hisama, 2019[37]; The New York Times, 2019[39]). The test results can also cause emotional distress – in the case of a positive result – or even patient harm – should a negative result appear which in fact is later found to be inaccurate (The New York Times, 2019[39]).

Finally, BRCA 1/2 testing does not lead to a straightforward treatment or preventive solution. For example, preventive mastectomy may not be warranted in all circumstances, and the advantage of such an approach would need to be carefully weighed against other factors such as previous cancer diagnoses or family history (McGee et al., 2017[40]; Yang et al., 2016[41]; Boccardo and Gentilini, 2016[42]). Assessing the appropriate preventive or treatment strategy should happen with appropriate input and guidance from medical professionals (Singer et al., 2019[43]; Rutgers et al., 2019[44]); the risk of DTG genetic tests is that this support is not readily available.

Sources: Kuchenbaecker, K. et al. (2017[31]) , "Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers", *JAMA*, Vol. 317/23, p. 2402, http://dx.doi.org/10.1001/jama.2017.7112; Howlader, N. et al. (2017[32]), *SEER Cancer Statistics Review, 1975-2014, National Cancer Institute*, SEER, Bethesda, MD., http://seer.cancer.gov; Walsh, T. et al. (2017[33]), "Genetic Predisposition to Breast Cancer Due to Mutations Other Than BRCA1 and BRCA2 Founder Alleles Among Ashkenazi Jewish Women", *JAMA oncology*, Vol. 3/12, pp. 1647-1653, http://dx.doi.org/10.1001/jamaoncol.2017.1996; Liede, A. et al. (2018[34]), "Risk-reducing mastectomy rates in the US: a closer examination of the Angelina Jolie effect", *Breast Cancer Research and Treatment*, Vol. 171/2, pp. 435-442, http://dx.doi.org/10.1007/s10549-018-4824-9; Evans, D. et al. (2014[35]), "The Angelina Jolie effect: how high celebrity profile can have a major impact on provision of cancer related services", *Breast Cancer Research*, Vol. 16/5, p. 442, http://dx.doi.org/10.1186/s13058-014-0442-6; Lee, J. et al. (2017[36]), "Influence of the Angelina Jolie announcement and insurance reimbursement on practice patterns for hereditary breast cancer", *Journal of Breast Cancer*, Vol. 20/2, pp. 203-207, http://dx.doi.org/10.4048/jbc.2017.20.2.203; Schleit, J., L. Naylor and F. Hisama (2019[37]), "First, do no harm: direct-to-consumer genetic testing", *Genetics in Medicine*, Vol. 21/2, pp. 510-511, http://dx.doi.org/10.1038/s41436-018-0071-z; Breast Cancer Action (2018[38]), *FDA-Approved Breast Cancer DNA Test by 23andMe May do More Harm than Good | Breast Cancer Action*, https://bcaction.org/, https://bcaction.org/2018/03/07/fda-approved-breast-cancer-dna-test-by-23andme-may-do-more-harm-than-good; Schleit, J., L. Naylor and F. Hisama (2019[37]), "First, do no harm: direct-to-consumer genetic testing", *Genetics in Medicine*, Vol. 21/2, pp. 510-511, http://dx.doi.org/10.1038/s41436-018-0071-z; The New York Times (2019[39]), *Don't Count on 23andMe to Detect Most Breast Cancer Risks, Study Warns*, https://www.nytimes.com/2019/04/16/health/23andme-brca-gene-testing.html (accessed on 18 April 2019); McGee, J. et al. (2017[40]), "Risk of breast cancer after a diagnosis of ovarian cancer in BRCA mutation carriers: Is preventive mastectomy warranted?", *Gynecologic Oncology*, Vol. 145/2, pp. 346-351, http://dx.doi.org/10.1016/J.YGYNO.2017.02.032; Yang, Y. et al. (2016[41]), "The rise in bilateral mastectomies: Evidence, ethics, and physician's role", *The Breast*, Vol. 29, pp. 160-162, http://dx.doi.org/10.1016/J.BREAST.2016.07.024; Boccardo, C. and O. Gentilini (2016[42]), "Contralateral risk reducing mastectomy in patients with sporadic breast cancer. Benefits and hazards", *European Journal of Surgical Oncology (EJSO)*, Vol. 42/7, pp. 913-918, http://dx.doi.org/10.1016/J.EJSO.2016.04.054; Singer, C. et al. (2019[43]), "Genetic counselling and testing of susceptibility genes for therapeutic decision-making in breast cancer—an European consensus statement and expert recommendations", *European Journal of Cancer*, Vol. 106, pp. 54-60, http://dx.doi.org/10.1016/J.EJCA.2018.10.007; Rutgers, E. et al. (2019[44]), "European Breast Cancer Council manifesto 2018: Genetic risk prediction testing in breast cancer", *European Journal of Cancer*, Vol. 106, pp. 45-53, http://dx.doi.org/10.1016/J.EJCA.2018.09.019.

In the United States, '23andMe' is perhaps the best-known DTC genetic test, which provides information about ancestry, as well as about health predispositions to a variety of condition such as type 2 diabetes, BRACA1/2, celiac disease, late-onset Alzheimer's, and Parkinson's disease (23andme, 2019[45]). 23andme tests can also give information about 'how genes play a role in well-being and lifestyle choices', for example sleep or weight, as well as carrier status for cystic fibrosis, sickle cell anaemia, or hereditary hearing loss. Background information on carrier status testing and genetic health risk testing is provided, including encouragement to speak to a genetic counsellor before and after testing, but this is not required and 23andMe does not provide this service. 23andMe is regulated as a medical device by the United State's FDA, setting requirements for analytical performance, clinical validity, and access to genetic counselling services (Fukuda and Takada, 2018[27]), although in a number of other countries where 23andMe is operating it is not regulated as a medical device.

Given the diversity of regulation across countries for this single company, it is unsurprising that there is significant diversity between OECD countries when it comes to legal regulations for DTC genetic testing services. In Austria, France, Germany and Switzerland DTC genetic testing was, in 2018, prohibited, although at the time of writing some international DTC genetic testing companies were shipping to all these states. Regulation in Belgium, Canada, Japan, and the United Kingdom does not cover these tests, while in South Korea and the United States limitations are in place (Table 3.5).

Table 3.5. Laws and policies on regulating health-related DTC genetic testing without health professionals' involvement, 2018

Country	Legal regulations for DTC Genetic testing services
Austria	Prohibited
Belgium	No direct application
Canada	No direct application
France	Prohibited
Germany	Prohibited
Japan	No direct application
Portugal	Prohibited
South Korea	Limitations on certain genetic tests
Switzerland	Prohibited
United Kingdom	No direct application
United States*	Limits certain genetic testing including requiring a premarket review

Source: Adapted from Fukuda, R. and F. Takada (2018[27]), "Legal regulations on health-related direct-to-consumer genetic testing in 11 countries", Kitasato Med J, Vol. 48, pp. 52-59, http://mlib.kitasato-u.ac.jp/homepage/ktms/kaishi/pdf/KMJ48-1/KMJ48-1p52-59.pdf.

The potential risks of weak regulation of DTC genetic tests should not be underestimated, both in terms of the range of tests which are permitted, and the accuracy of the results. To take the example of BRCA1/2 testing, which is not currently permitted in Korea (see 3.4.2), criticisms have included that testing may encourage medically unnecessary preventive surgeries, and that existing tests cover only a narrow range of known mutations potentially leading to an under-estimation of risk, or that tests are not accurate (Breast Cancer Action, 2018[38]; Schleit, Naylor and Hisama, 2019[37]). Schleit et al. (2019[37]) detail the experience of one woman with a family history of breast cancer, for whom a DTC test did not show up positively for BRCA markers, but for whom a clinical molecular genetic test showed a genetic risk. Some studies have suggested that discrepancy in DTC and clinical genetic testing is relatively commonplace (Tandy-Connor et al., 2018[46]).

3.4.2. DTC genetic testing availability and regulation in Korea

In June 2016, Korea allowed direct-to-consumer (DTC) genetic testing on 42 genes (Jeong, 2017[47]), see also Table 3.6. Direct-to-consumer testing in Korea is regulated under the Bioethics and Safety Act, under provisions for testing undertaken other than in a medical institution (see Box 3.2, Korea's Bioethics and Safety Act). Regulation of DTC functions under a 'positive list' for genetic tests that covers genetic test items that can be conducted directly by a genetic testing institution, other than a medical institution. Limitations are placed on certain genetic tests, for example tests predicting physical characteristics or personality traits, tests lacking in scientific evidence, or tests which are forbidden by Presidential Decree following review by the National Committee (Fukuda and Takada, 2018[27]).

Currently, the DTC genetic tests allowed in Korea focus on many cosmetic dimensions (for instance hair loss, skin elasticity, hair thickness). However, other tests such as those showing an odds-ratio for BMI level, for cholesterol or blood pressure, could give consumers some information about their health status or "risks". However, it is not clear how useful this information is. At best, this information could encourage healthier behaviours, but at worst, could constitute a serious public health risk if it leads people to under- or over-estimate their susceptibility to particular health conditions, which might in turn them to engage in risky behaviours or undertake unwarranted medical procedures.

Table 3.6. Genetic test items that can be conducted directly by a genetic testing institution (outside of medical institutions), 2018

Direct to consumer tests allowed in Korea showing what the DTC tests for, the number of genes included in the test, and the individual genes

Test Item (Number of Genes)	Gene
BMI(3)	FTO, MC4R, BDNF
Concentration of triglycerides(8)	GCKR, DOCK7, ANGPTL3, BAZ1B, TBL2, MLXIPL, LOC105375745, TRIB1
Cholesterol(8)	CELSR2, SORT1, HMGCR, ABO, ABCA1, MYL2, LIPG, CETP
Blood sugar(8)	CDKN2A/B, G6PC2, GCK, GCKR, GLIS3, MTNR1B, DGKB-TMEM195, SLC30A8
Blood pressure(8)	NPR3, ATP2B1, NT5C2, CSK, HECTD4, GUCY1A3, CYP17A1, FGF5
Pigmentation(2)	OCA2, MC1R
Hair loss(3)	chr20p11(rs1160312, rs2180439), IL2RA, HLA-DQB1
Hair thickness(1)	EDAR
Skin aging(1)	AGER
Skin elasticity(1)	MMP1
Vitamin C concentration(1)	SLC23A1(SVCT1)
Caffeine metabolism(2)	AHR, CYP1A1-CYP1A2

Source: Information supplied to the OECD by the Korean Authorities.

Even following the 2016 decision by Korea to allow DTC genetic testing on a limited number of genes, a survey the same year indicated that enthusiasm for genetic information amongst Korean consumers was significant (Jeong, 2017[47]). This survey suggested that Korea consumers were also interested in having access to a wider range of genetic information than the existing 42 gene DTC genetic tests permitted.

In early 2019, the Korean Government announced a significant expansions of allowed DTC genetic tests. From the initially allowed DTC tests (Table 3.6), the expansion will cover 13 diseases, including coronary artery disease, atrial fibrillation, hypertension, type-2 diabetes, stroke and osteoarthritis, prostate, colorectal, stomach, lung and liver cancer, Parkinson's disease and macular degeneration (Korea Biomedical Review, 2019[48]). This move followed a request by the biotech firm Macrogen for expansion in permitted DTC genetic testing; the government declined the request to include breast cancer and dementia testing, and suggested that further review was needed on testing for late-onset Alzheimer's. Initially the expansion will be to a 'demonstration project' for 2 000 adults, across two years, after which the project will be reviewed. Easing of the DTC market was anticipated, by the Korean Labor institute, to lead to an expansion in sales for the industry of 503%, a growth in investment of 458%, and a growth in jobs of 45% over ten years (Business Korea, 2019[49]).

While legislation in Korea limits the genes that can be tested, quality control of DCT genetic tests appears to be weak. While genetic tests within the health system are relatively tightly regulated, licensing requirements for DTC are less strict, and quality controls are weaker. In Korea DTC genetic tests are not regulated as medical technologies.

Weak legislation means that the accuracy of DTC genetic tests cannot necessarily be assured. Some medical professionals, and research papers, have raised concerns about the accuracy of DTC genetic tests (Kim et al., 2014[50]; Jeong, 2017[47]; The New York Times, 2019[39]; Moscarello et al., 2019[51]), and anecdotal reports have suggested that private DTC genome testing generated results inconsistent with those of medical laboratories in Korea. With the broadening of permitted genetic testing to include a significant number of health conditions consequences of inaccurate testing could be considered to increase. Some inherent risks based on methodology should also be considered, for example the ethnic representativeness of comparator populations in the Korean context (Kim et al., 2014[50]; The New York Times, 2019[39]).

3.4.3. Weak regulation of DTC genetic testing could constitute a privacy risk

The potential privacy risks from DTC genetic test consumers should be considered, especially given that regulation of providers at present appears to be weak (Hendricks-Sturrup, Prince and Lu, 2019[52]).

Firstly, consumers are potentially sharing significant amounts of sensitive personal medical data with a private company, for which monitoring and quality assurance is currently weaker than for traditional medical providers. This data should be protected under the Personal Information Protection Act and the Bioethics and Safety Act. However, without sufficient steps to secure personal data, leaks and hacks become more likely. While the legal framework in Korea should protect consumer's data, it is not clear that DTC genetic testing companies are checked for their data protection standards, or would be held to the same standards as medical institutions when it comes to data handling.

Secondly, consumers' data may be used in a way that they were not fully aware of. Jeong (2017[47]) points to a potential regulatory loophole, wherein a company could analyse genes or store genes not currently allowed to be tested or stored, and/or share or sell analysis results with third parties. Although the current legislative framework prohibits such activity, the current regulatory and monitoring architecture may not be sufficient to dissuade or catch any such activities.

Even without such actions, consumers may consent to the use of their data in a way that they did not fully understand, perhaps given lengthy terms and conditions or disclaimers which were difficult to fully grasp. DTC genetic testing can generate huge genetic databases, which have potential to be extremely valuable for research, including for private companies. Databases might include not just the genetic testing results, but also the (linked or otherwise) results of any background information that the consumer has filled out. For example, 23andMe has established significant partnerships with major pharmaceutical companies (Check Hayden, 2017[53]; Time Magazine, 2018[54]; GSK, 2018[55]; Forbes, 2018[56]).

3.4.4. Potential risk to consumers and the health system from DTC genetic testing

Direct-to-consumer testing is a growing industry, and it appears that the situation in Korea is no exception. Consumer enthusiasm is high, and companies are growing and multiplying to meet that demand. Proponents of DTC genetic testing defend both a normal curiosity about heritage, ancestry, and health status, and even point to the potentially positive impact on health behaviours. However, understanding of the test results is not straightforward, and there are several ethical considerations that should be considered. Even if DTC genetic testing was consistently accurate, the risk of presenting individuals with information that they do not understand or that they cannot act upon, could result in considerable emotional distress.

First, there is good reason to question the ethics of making widespread testing available for diseases for which there is not (yet) an effective cure, especially if support to interpret and understand the consequences of the results is not systematically in place (Roberts and Uhlmann, 2013[57]). Second, presenting individuals with information that they do not understand, that is difficult to interpret, or which needs further contextual information to improve understanding, risks causing emotional distress (Rutgers et al., 2019[44]; Singer et al., 2019[43]; Wang et al., 2018[58]); a 2018 study in the Netherlands found that individuals with lower knowledge of genetic principles were more likely to consider and/or intend to undergo DTC genetic testing (Stewart et al., 2018[59]). In Korea, some DTC genetic tests show odd-ratios between the risk of developing a disease based on genetic variants, and population risks, to present a relative risk ratio. For even an educated and relatively well-informed consumer, such information can be extremely hard to understand.

In addition, the potential additional burden to the health care system, generated by an expanded DTC genetic test market, should also not be under-estimated. The health system and medical professionals specifically may come under increasing pressure to make secondary testing available to check DTC genetic test results (Moscarello et al., 2019[51]), interpret results, or even provide care that may not be medically necessary. Recent evaluations of the DTC genetic testing market in the United States have suggested that 20-30% of consumers share their genetic test data with health care providers (Wang et al., 2018[58]; Stewart et al., 2018[30]); if DTC

genetic tests in Korea grew to similar levels of popularity as in the United States, and consultation with health care providers followed a similar pattern, this would constitute a significant extra burden on the health system. A 2016-17 survey in Korea suggested that Korean physicians expressed concerns about the impact of DTC genetic tests, and appeared sceptical about potential expansion (Eum et al., 2018[60]).

Taken to its most extreme, a test suggesting a protective trait for certain diseases could even lead individuals to engage in high-risk behaviours, for example in terms of tobacco consumption or sedentarism. The public health benefits of a genetic test which suggests a 'low risk of becoming obese', in a context where obesity rates are rising, seems negligible.

3.5. Strengthening the use of genomics for public health in Korea

3.5.1. Develop a national strategy on precision medicine

Precision medicine is, clearly, an expanding field in Korea. The use of genetic testing in the medical field seems to be growing, and appetite for genetic testing amongst Korean consumers appears high. In many respects Korea appears to be ahead of OECD peers when it comes to managing the growing field of precision medicine. The legislative framework for genetic testing appears robust, and DTC genetic tests also fall under these regulations. Increases in DTC genetic tests are being approached in an appropriately cautious and stepwise way.

However, at present it does not appear that Korea has an overarching strategy in terms of harnessing the potential of precision medicine, increasing its positive impact on public health, or managing impacts on the health system. Korea should look to develop an overarching National Strategy for Precision Medicine, which would include consideration of issues such as:

- The particular characteristics of the Korean health system should be taken into consideration. Notably the relatively low rate of medical professionals, high rate of consultations, and absence of a primary care gatekeeper function; the potential impact of increased demand for care, for examine following DTC tests, from the Korean population should be considered;
- The need for a greater number of medical specialists in genetic medicine, and building genetic literacy amongst Korean medical professionals in general, for instance by including precision medicine as part of basic medical education or continuing education;
- Developing guidelines to clearly identify genetic tests that demonstrated both clinical validity and utility, and help clinicians to make informed decisions for their usage;
- Systematically evaluating the cost-effective of genetic tests and their use for prevention;
- Ensuring that cost-sharing requirements currently in place for medically-prescribed genetic tests do not cause inequalities in health care access.

Numerous other OECD countries have developed national strategies for precision medicine (or, for "genetic medicine" or "genomic medicine"), and could offer models for Korea to follow (see Box 3.4). In both Denmark and France the development of a national strategy was preceded by a stock-taking effort to understand the existing provision of, need for, and implications of expanding precision medicine. It would be important, as was the case in Denmark and France, for Korea to develop such a strategy through a multi-stakeholder consultation process. The objectives of different stakeholders may differ significantly: for example, the Korean population may see genetic testing as far more beneficial than Korean physicians, or Korean oncologists could be worried about exploding demand for unnecessary preventive interventions such as mastectomies, while patient groups for rare cancers might see genetic testing as a key weapon in better diagnosis and care. The stakeholder group developing Korea's National Strategy on Precision Medicine should have high level endorsement from the Korean government, and should also include stakeholders such as physicians and nurses, genetic counsellors, patient and/or consumer groups, researchers in the field, and representatives of industry.

Box 3.4. National strategies for precision medicine – Australia, Denmark, France and the United Kingdom

The Australian Government announced the Genomics Health Futures Mission (GHFM) in May 2018, backed by a budget of AUD 500 million over 10 years, the GHFM is intended to help Australians live longer and better by funding health and medical research into improved testing, diagnosis, and treatment (Australian Government Department of Health, 2019[61]). The GHFM is also intended by Australia to be an opportunity to promote and build on the country's reputation as a leader in the field, both in terms of research and the implementation of genomic medicine. Initial investments under the GHFM have included AUD 20 million in a pilot research study of reproductive carrier screening for genetic conditions affecting children, AUD 20.4 million to produce the largest ever cancer proteome dataset, AUD 33.7 million a research projects grant round to answer complex genomics research questions in cancers including ethical, legal and social issues related to the use of genomics in health care, and AUD 32 million large scale flagship projects in pathogen genomics. In each area, there is also a focus on translating findings into health care usage, for example the pilot study of reproductive carrier screening is designed to inform how such screening can best be equitably and usefully offered to Australians, while the investment in pathogen genomics specifically focuses on demonstrating the clinical and/or public health utility, cost effectiveness, and capacity for research translation of pathogen genomics in mainstream healthcare. An independent Expert Advisory Committee is overseeing the GHFM and providing specialist knowledge and implementation advice to best support the objectives of the GHFM.

In France, the 'France Genomic Medicine Plan 2025' (*France Médecine Génomique Plan 2025)* was established by the French government in 2016 and will run until 2025, and is being coordinated by AVIESAN (*Alliance national pour les sciences de la vie et de la santé*, National alliance for human sciences and health) under the supervision of the Prime Minister. The Plan was developed with an ambition of assessing the current availability of, and prospect for evolution over ten years, access to diagnostic genetics in France. The plan was developed with input from representatives of genetic research, the health system and health insurance system, industry, research agencies, French central ministries, and a number of major universities. The plan identifies four major challenges (a potential revolution in public health care; the need for scientific and clinical research; technological pressures in particular around storing, sharing, and using data; and the economic impact) and three major objectives. The objectives are, firstly, to position France as an international leader in personalised and precision medicine, secondly to integrate genetic medicine into health care delivery and care, and thirdly the development of a genomic medicine sector capable of driving innovation and economic growth, including industry as well as academic and public partners (AVIESAN, 2016[62]). So far, the France Genomic Medicine Plan 2025 has led to the establishment of two high volume genetic sequencing platforms: SEQOiA supported by a coalition of hospitals (Public Assistance - Paris Hospitals, APHP), and research institutions Institut Curie and Institut Gustave Roussy; and AURAGEN supported by the Civils Hospices of Lyon, Grenoble University Hospital, Saint-Etienne University Hospital, Clermont-Ferrand University Hospital, the Léon Bérard Center, Jean Perrin Center and the Loire Cancer Institute (French Government, 2017[63]).

In Denmark, the National Strategy for Personalised Medicine 2017-2020 was established by the Danish National Government and the Danish Regions in 2017. The strategy focuses on establishing better and more targeted care for patients, stronger ethical, legal and safety regulations regarding the use of genetics in health care, the establishment of joint governance structures and stronger collaboration between health care and research in this field, building safe, collaborative and coherent technological infrastructure, and initiating relevant research and development projects. The Strategy was backed by an initial allocation of 100 million DKK (~16.1 million USD), with the expectation that developments

would be co-financed by public research resources, regional resources, and private actors (Danish Ministry of Health, 2017[64]).

The development of the plan was informed by a preliminary analysis project, in 2016, which assessed the professional, technical, ethical and financial implications of development of a Danish programme for personalised medicine. This analysis was undertaken by a steering committee of the Danish Ministry of Health (Chair), Danish Regions (Vice-chair), Ministry of Higher Education and Science, Ministry of Business and Growth and Ministry of Finance, and had a reference group which included representatives from health care, research, patient groups, academia and industry. The analysis considered the ethical and legal aspects related to using biological material and personal information, considered international experiences, and gathered Danish citizen's views towards personalised medicine and genetic tests (Danish Ministry of Health, 2017[65]).

The United Kingdom announced a new 'National Genomic Health Care Strategy' in February 2019, which aims to deliver a 'predictive, preventative and personalised health and care service for people with rare diseases'. Targeted to rare conditions, this strategy builds on the United Kingdom's existing projects in the area of genetic medicine, which includes offering whole genome sequencing to every adult and child with certain cancers and rare genetic conditions, and large-scale projects such as the 100 000 Genomes Project, and the NHS National Genomic Medicine Service. The strategy includes care delivery dimensions, such as a dedicated person to co-ordinate care, and detailed information on the condition, treatment regime and key expert contacts (Department of Health and Social Care (United Kingdom), 2019[66]).

Other OECD countries, including Canada, China, Germany, the United Kingdom, the United States have also national personalised medicine plans (see (OECD, 2017[6]; Garrido et al., 2018[67]; OECD, 2019[68]).

Sources: Australian Government Department of Health (2019), *Genomics Health Futures Mission*, https://www.health.gov.au/initiatives-and-programs/genomics-health-futures-mission (accessed on 29 January 2020); AVIESAN (2016), *France Médicine Génomique 2025*, Alliance nationale pour les sciences de la vie et de la santé, Paris, http://www.gouvernement.fr/sites/default/files/document/document/2016/06/22.06.2016_remise_du_rapport_dyves_levy_-_france_medecine_genomique_2025.pdf (accessed on 22 April 2019); French Government (2017), "Plan & France médecine génomique 2025; : lancement des 2 premières plateformes | Gouvernement.fr", https://www.gouvernement.fr/partage/9344-plan-france-medecine-genomique-2025-lancement-des-2-premieres-plateformes (accessed on 22 April 2019); Danish Ministry of Health (2017), *Preliminary Personalised Medicine Analysis 2016*, https://www.sum.dk/English/Healthcare-in-Denmark-An-Overview/Personalised-Medicine/Preliminary-Personalised-Medicine-Analysis-2016.aspx (accessed on 22 April 2019); Department of Health and Social Care (United Kingdom) (2019), "NHS must lead the world in genomic healthcare - GOV.UK", *gov.uk*, https://www.gov.uk/government/news/health-minister-nhs-must-lead-the-world-in-genomic-healthcare (accessed on 22 April 2019); OECD (2017), *New Health Technologies: Managing Access, Value and Sustainability*, OECD Publishing, Paris, https://dx.doi.org/10.1787/9789264266438-en; Garrido, P. et al. (2018), "Proposal for the creation of a national strategy for precision medicine in cancer: a position statement of SEOM, SEAP, and SEFH", *Clinical & Translational Oncology*, Vol. 20/4, p. 443, http://dx.doi.org/10.1007/S12094-017-1740-0; OECD (2019), *OECD Reviews of Public Health: Chile: A Healthier Tomorrow*, OECD Publishing, Paris, https://dx.doi.org/10.1787/9789264309593-en.

3.5.2. Ensure that quality assurance and regulation are robust

Legislation around which actors can prescribe, undertake and finance (a limited number of) genetic tests appears to be well in-place in Korea. Equally, data privacy legislation should cover the data generated by the tests. However, most of the tests prescribed by medical institutions are processed by a limited number of private laboratories. At present Korea does not have a quality assurance system which ensures the safety and validity of these processes. Additionally, specific clinical guidelines to ensure quality at the point of clinical testing may be warranted. Establishing a comprehensive regulatory framework would make Korea a relative leader in this field, and is a process that could be undertaken in tandem with the

development of the National Strategy for Personalised Medicine, and with input from all relevant national (and international) agencies.

The WHO and the OECD give general guidance regarding the quality assessment of genetic tests, which would need to be adapted and specified to the Korean context and the evolving field (OECD, 2007[69]; WHO, 2016[70]):

- Quality should be assured throughout the process, from the pre-clinical phased including establishing whether a test is necessary, obtaining consent, and providing counselling, to sample retrieval, analysis in the laboratory, and interpretation of the results and sharing with the patients;
- Steps should be taken to ensure analytic validity (competency of the laboratory and assessment against standardised samples); clinical validity (predictiveness) of the test; and clinical utility;
- The regulatory structure for genetic tests should include 'what it ultimately means to interpret test results accurately and fairly, and who determines the standards to which the professionals, from lab technicians to counsellors, should be held… how, and by whom, these standards are maintained or enforced';
- Steps to measure the performance of laboratories, such as quality assurance accreditation, should be considered, and quality checks should extend to reporting practices;
- Education and training practices for laboratory personnel are key.

3.5.3. Strengthen data linkages

To build on its already-strong health data information system, in the further development of precision medicine Korea should look to develop an integrated system of genome information with medical and patient information.

Going forward, data linkage should be a priority pillar of the Korean Government's approach to precision medicine. While the ethical questions around the management and use of genetic data must remain at the forefront, the field of precision medicine is an area where big data could be game-changing (Wordsworth et al., 2018[71]). For example, genomic information can be stored for research only, but cannot be linked to the HIRA and National Health Insurance databases, and is difficult to use in routine clinical care.

Additionally, despite the fact that the Korean Government appears to be strongly committed to Korea being a leader in genetic research, current data legislation strongly restricts sharing of (even de-identified) health data, which may limit Korea's capacity to participate in potentially fruitful international collaborative efforts (Wordsworth et al., 2018[71]).

3.5.4. Focus on building on genetic literacy amongst medical professionals and the Korean population

As the importance of precision medicine in Korean health care grows, Korea should look to improve 'genetic literacy' amongst Korean health care professionals and the Korean population. Already there are signs that despite enthusiasm for DTC genetic tests in Korea (Jeong, 2017[47]), a small survey of the Korean population revealed low awareness of genetic risk factors for disease (Lee et al., 2018[72]). Another survey suggested that Korean cancer patients over-estimated the potential benefits of genetic testing, but that greater access to genetic testing was viewed in a strong positive light by general respondents (Eum et al., 2018[60]).

Improving genetic literacy amongst health care professionals would anticipate precision medicine playing a growing role in diagnosis in treatments in the decades, if not years, to come. Up-skilling professionals would also help them meet the increasing generic inquiries coming from patients, possibly prompted by DTC genetic tests that they had undertaken. Finally, improving professionals' genetic literacy could

harness understandings of genetic and hereditary disease risks to improve preventive care without necessitating and expansion in testing coverage (see Box 3.5).

Improving population health literacy can improve individuals' capacity to judge the pros and cons of different treatment options, reduce hospital use, adopt better preventive measures, and reduce health care costs (Moreira, 2018[73]). Low health literacy can also be expected to reduce consumers' ability to interpret DTC genetic tests, and understand how this information relates to their health behaviours, status, and care needs.

Korea ought to look for different ways to improve the 'genetic literacy' of health care professionals, and the Korean population. When it comes to health professionals, inclusion of modules in formal education or continuing education, or distribution of informational materials in the work place, or checks as part of quality assurance could be considered.

For the Korean population, a first step would be ensuring that easy to understand information about precision medicine, genetic tests prescribed by the health system, and the advantages and limitation of the existing range of precision medicine. Tools and information should be easy to read and understand (Wang et al., 2011[74]). Additionally, DTC genetic test companies, especially those included in the new suite of DTC genetic tests, should be required to provide similar information about the advantages, limitations and risks of the tests, clear information to help with the interpretation of test results, and details of genetic counselling services.

Box 3.5. Tools to build literacy around disease risk for health providers and the general population

There are ways to leverage understanding of genetic and inherited disease risks without relying primarily on genetic testing. Family health history-based risk assessment can be used in primary care-equivalent settings, or even as a population education approach, to improve understanding of risk (Wu et al., 2019[75]).

A number of tools that can be embedded in primary practice, or for general access, can help understanding of family health history and disease risk. One example is MeTree, developed by the Duke Center for Applied Genomics and Precision Medicine, which gathers data entered by patients, for example on diet, exercise and smoking, but also on personal and family health history on cancer, cardiovascular syndromes, and other conditions (Wu et al., 2014[76]; Orlando et al., 2014[77]; Wu et al., 2013[78]; Wu et al., 2019[75]). The information collected can be accessed by the provider, but the tool also providers action-orientated information to the patient, including potentially relevant follow-up genetic test and pharmacogenomic tests.

Other tools are freely accessible online, and targeted at the general population to help building family health history for discussion with primary health providers. The Centres for Disease Control and Prevention have the "My Family Health Portrait" tool, endorsed by the United States Surgeon General, which gathers basic family history in 15 to 20 minutes, that is then collated in a format that is easily shared and discussed with health care providers and is compatible with integration into electronic health records (Centers for Disease Control and Prevention, 2018[79]). Other tools, including some recommended by the United States' National Human Genome Research Institute such as Family Health*Link*, give individuals an estimation of disease risk by reviewing patterns of disease such as cancer and heart disease in the family.

Sources: Wu, R. et al. (2014), "Quality of family history collection with use of a patient facing family history assessment tool", *BMC Family Practice*, Vol. 15/1, p. 31, http://dx.doi.org/10.1186/1471-2296-15-31; Orlando, L. et al. (2014), "Implementing family health history risk stratification in primary care: Impact of guideline criteria on populations and resource demand", *American Journal of Medical Genetics Part C: Seminars in Medical Genetics*, Vol. 166/1, pp. 24-33, http://dx.doi.org/10.1002/ajmg.c.31388; Wu, R. et al. (2019), "Implementation, adoption, and utility of family health history risk assessment in diverse care settings: evaluating implementation processes and impact with an implementation framework", *Genetics in Medicine*, Vol. 21/2, pp. 331-338, http://dx.doi.org/10.1038/s41436-018-0049-x; Wu, R. et al. (2013), "Patient and primary care provider experience using a family health history collection, risk stratification, and clinical decision support tool: a type 2 hybrid controlled implementation-effectiveness trial", *BMC Family Practice*, Vol. 14/1, p. 111, http://dx.doi.org/10.1186/1471-2296-14-111; Centers for Disease Control and Prevention (2018), *My Family Health Portrait|Public Health Genomics Knowledge Base*, https://phgkb.cdc.gov/FHH/html/index.html (accessed on 19 April 2019).

In terms of genetic counselling, this is considered by many countries as a critical part of clinical care, both before and after genetic countries, and is mandatory in countries such as Austria, Australia, France, Germany, Portugal and Switzerland (see Table 3.5). In Korea, genetic counselling is not required for patients undergoing genetic testing, and this may be an area where further examination and/or inclusion in clinical guidelines is warranted. Genetic counselling is not yet institutionalised in Korea.

3.5.5. Take a cautious approach to DTC genetic testing

As set out earlier in this chapter, in early 2019 the Korean Government elected to expand the DTC genetic tests allowed in the country, subject to a two year demonstration period. This expansion includes allowing tests covering 13 diseases, including diabetes, several cancers, Parkinson's disease, and macular degeneration.

Following this decision, and in the context of a Korean population who appear enthusiastic about the expansion in the range of DTC genetic tests available (Jeong, 2017[47]; Eum et al., 2018[60]), the Korean Government should nonetheless proceed with caution. The potential risks to consumers and the health system from DTC genetic testing, including privacy risks, ethical risks, potential exposure of individuals to distressing information which they may struggle to understand, and possible increased strain on the health system, should all be given serious consideration during this demonstration period, and in any further decisions to expand the DTC genetic test market. Additionally, robust processes ought to be put in place to ensure the quality of DTC genetic tests, protection of consumer data, the comprehensibility of information about the tests and about the results.

3.5.6. From a public health perspective, 'traditional' approaches to preventing ill-health still have the strongest evidence-based

In a relatively small number of cases, precision medicine can have a transformative impact. For example, WGS can be a powerful tool for diagnosing rare infant diseases, and understanding of how some gene mutations can cause breast cancer can strengthen the potential of preventive interventions and the effectiveness of treatments. However, the impact of precision medicine for public health, prevention, or even diagnosis remains narrow. Precision medicine approaches cannot, at this stage, form the basis of a country's public health or preventive strategy.

The evidence base for 'traditional' approaches to public health and disease prevention, meanwhile, is far more robust. Interventions such as those detailed in Chapters 1 and 2, for instance restricting alcohol sales, using educational approaches to change drinking patterns, or reviewing pricing and taxation policies, have been well-established as evidence-based and in many instances cost-effective.

Conclusion

In Korea, genomic medicine is an exploding and popular field: genomic research, genetic testing and precision medicine, and direct-to-consumer genetic testing, are significant areas of policy attention, while in terms of genomic research, Korea has the biggest biobank in Asia and one of the biggest in the world. Genetic testing is widespread and increasing, both for hereditary (mostly infant) diseases, for some cancers where there is a strong family history, and following cancer diagnoses to personalise treatment. A regulatory framework has been developed for these tests, but quality assurance of private testing laboratories and training for health professionals are less well-developed and health coverage does not appear to be keeping pace with demand from patients and clinicians. The cost-effectiveness of widespread use of genetic testing to personalise treatment (in particular cancer) does not appear to have been established. The area which generates the most concern when it comes to genomic medicine in Korea is the booming field of direct-to-consumer tests (DTC) genetic tests. At present the Korean Government is proceeding in a cautious and stepwise fashion, which seems appropriate. Careful consideration should be given to the potential risks to DTC test consumers, and impacts on the health system, following increased availability of genetic testing for health risks.

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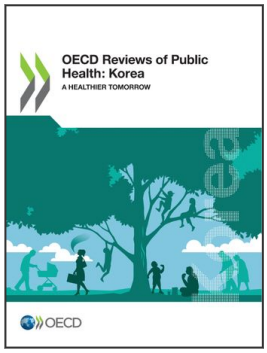

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