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Regulating the unknown
A guide to regulating genomics for health policy-makers

Gemma A Williams
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**Public Health Legislation**

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The authors and editors are grateful to the reviewers who commented on this publication and contributed their expertise.
Foreword

The volume and availability of genomic data and information has grown exponentially in the past three decades, bringing with it new insights that have transformed our understanding of human health and disease. While we are some way off from realizing the full potential of genomics in the health sector, these advances are slowly being translated into targeted clinical care for some of the most pressing health issues of our time, such as cancer and cardiovascular diseases. In the future, ever greater insights from genomics hold the potential to usher in a new era of personalized medicine that will have a major impact on health care.

While these rapid advances in genomics hold huge potential to transform health and health care for the better, they nevertheless raise a number of critical questions over ethical use, privacy and security. How can the rights of patients and research participants that supply genomic data be fully protected? Who can access data and how can it be prevented from falling into the hands of those that may use it for purposes against the interests of the data subjects? How can governments capture the wide range of benefits from genomic information? These questions and many more must be answered by policy-makers before the use of genomic insights in the health sector can become routine and widespread.

I am therefore pleased to introduce this policy brief that considers many of the complex ethical and legal challenges that are brought to the fore by genomics. We explore a number of best-practice examples of how these issues have already been addressed through legislation such as the GDPR and other protective mechanisms in Europe and further afield. We nevertheless show that many regulatory and enforcement challenges remain ahead of us to ensure that advances in genomics are used to their full potential on the basis of shared European values. Importantly, we demonstrate that genomics is a dynamic and shared enterprise that must involve the full and informed participation of patients, the public, clinicians, researchers, private companies and governments in order to thrive. Finally, we show that much advancement in this area has relied on international collaboration and we must continue to facilitate cooperation in this area in order to seize many of the exciting opportunities that genomics may fashion for health care in the years ahead.

Liisa-Maria Voipio-Pulkki
Acknowledgments

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Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AI</td>
<td>artificial intelligence</td>
</tr>
<tr>
<td>BMA</td>
<td>(UK) British Medical Association</td>
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<tr>
<td>BMBF</td>
<td>Federal Ministry of Education and Research, Germany</td>
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<tr>
<td>CCM</td>
<td>National Centre for Disease Prevention and Control, Italy</td>
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<td>CE</td>
<td>Conformité Européenne</td>
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<tr>
<td>ctDNA</td>
<td>circulating tumour DNA</td>
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<tr>
<td>DTC-GT</td>
<td>direct-to-consumer genetic testing</td>
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<tr>
<td>EDPS</td>
<td>European Data Protection Supervisor</td>
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<tr>
<td>EEOC</td>
<td>Equal Employment Opportunity Commission</td>
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<tr>
<td>ELSI</td>
<td>ethical, legal and social implications</td>
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<td>ESHG</td>
<td>European Society of Human Genetics</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>FAIR</td>
<td>findable, accessible, interoperable, reusable</td>
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<tr>
<td>GA4GH</td>
<td>Global Alliance for Genomics and Health</td>
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<td>GDPR</td>
<td>General Data Protection Regulation</td>
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<tr>
<td>GeCIP</td>
<td>Genomics England Clinical Interpretation Partnership</td>
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<td>GENISAP</td>
<td>Italian Network for Public Health Genetics</td>
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<tr>
<td>GINA</td>
<td>Genetic Information Nondiscrimination Act</td>
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<tr>
<td>GP</td>
<td>general practitioner</td>
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<tr>
<td>GWAS</td>
<td>genome-wide association study</td>
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<tr>
<td>HTA</td>
<td>health technology assessment</td>
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<tr>
<td>iPAAC JA</td>
<td>Innovative Partnership for Action Against Cancer – Joint Action</td>
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<tr>
<td>IVD</td>
<td>in vitro diagnostic</td>
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<tr>
<td>IVDR</td>
<td>in vitro diagnostic regulation</td>
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<tr>
<td>KSI</td>
<td>Keyless Signature Infrastructure</td>
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<td>MRI</td>
<td>magnetic resonance imaging</td>
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<td>NCD</td>
<td>noncommunicable disease</td>
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<td>NCI</td>
<td>National Cancer Institute</td>
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<td>NGS</td>
<td>next-generation sequencing</td>
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<td>NHS</td>
<td>National Health Service</td>
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<td>NIH</td>
<td>National Institutes of Health</td>
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<td>NIPT</td>
<td>noninvasive prenatal testing</td>
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<tr>
<td>OECD</td>
<td>Organisation for Economic Co-operation and Development</td>
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<tr>
<td>PKU</td>
<td>phenylketonuria</td>
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<tr>
<td>PRECeDI</td>
<td>Personalized pREvention of Chronic Diseases consortium</td>
</tr>
<tr>
<td>PRS</td>
<td>polygenic risk scoring</td>
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<tr>
<td>R&amp;D</td>
<td>research and development</td>
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<tr>
<td>VUS</td>
<td>variants in genes with no known function or of uncertain significance</td>
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<tr>
<td>WGS</td>
<td>whole genome sequencing</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WMA</td>
<td>World Medical Association</td>
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Key messages

• Genomics can improve individual and population health outcomes, but making genomic data widely available creates ethical, legal and social challenges.

• Genomics reveals sensitive personal and familial information. This may improve prevention and treatment but means that, without regulation and other measures, at risk individuals can be discriminated against; or that those at low risk may opt out of public protection. This endangers the equity and solidarity that underpin European health systems.

• The possibility of data being misused by insurers, employers or others makes it essential that there is strong regulation of genomic data in research, in health care and more widely. Regulation needs to be proportionate to balance privacy and data security against the benefits of scientific advances and their translation into clinical practice.

• The 2018 European Union General Data Protection Regulation (GDPR) has transformed the way genomic data are processed and will impact research, clinical practice and national regulators, even beyond the EU.

• The benefits of genomics can only be realized if, in addition to effective regulation:
  – There is broad societal trust built by active dialogue and engagement.
  – All stakeholders, including industry are involved so that genomic initiatives engender confidence and align with societal values.
  – Wider information infrastructure and digitalization strategies are in place so that genomic data can be linked to other information without breaching public trust.
  – Policy makers are able to manage the costs of genomics-driven innovation and ensure that benefits give value for money, improve health and are fairly distributed.
Executive summary

Genomic information leads to insights that have the potential to improve health outcomes

Human genomics refers to the study of the entire human genome and the large amounts of corresponding data generated from it. The first sequencing of the human genome in 2003 spurred a revolution in understanding many of the complex pathways from genes to disease. Subsequent advances in genome sequencing technologies now mean that huge amounts of genomic information can increasingly be harnessed with the potential to improve health outcomes for individuals, groups or at the population level.

Systematic gathering of genome data and international cooperation in this field have increased in recent years

The scale of systematic gathering of genome data has increased in a number of countries in recent years and many genomic databases are involved in collaborations within international research projects. There are also initiatives, such as the ‘1+ Million Genomes’ declaration, signed in early 2018, to support collaborative efforts to translate genomic information into clinical practice and to use it for clinically impactful and relevant research.

Members of the public have direct access to commercial genetic tests, which bypasses the health system

Members of the public are increasingly able to access their health related genomic information through commercially available direct-to-consumer genetic testing (DTC-GT). This sometimes bypasses or has limited involvement of health professionals. Providing DTC-GT to consumers is therefore considered by some to be controversial due to concerns over clinical validity, utility, lack of genetic counselling and information, and potential harm to consumers, as well as the possibility of placing unnecessary additional strain on publicly funded health services, among other concerns. Nevertheless, many of these fears currently remain unfounded, with little evidence of unnecessary harm to consumers or health services. Moreover, the IVD medical devices providing information on the predisposition to a medical condition or a disease that are offered through the Internet to a natural or legal person established in the EU must comply with the rules set by the Regulation (Article 6) [82].

Developments in genomics raise important ethical, legal and social (ELSI) challenges at the individual level as well as for health systems and society as a whole

Many of the ethical, legal and social challenges related to the collection, storage and use of genomic information are not new and are similar to those for other health-related and personal information. However, genomics creates additional issues due to the sensitivity, longevity and usefulness of data collected that can be continually reanalysed and reinterpreted as new knowledge and big data analytic tools emerge and also because it reveals familial and not just personal information.

Further, in the absence of appropriate regulation and guidance, the exceptionally detailed type of information on individuals that is generated by genomics may pose a threat to privacy and undermine the concept of risk pooling and the values of universality, equity and solidarity that underpin European health systems by turning potential risks for everyone into likelihoods for a few.

Appropriate regulation is needed to reduce the risk of genomic data being misused and to ensure that the information it provides is used for the benefit of patients and wider society

Ultimately, the genie of new knowledge brought about by genomic advances cannot and should not be put back into the bottle due to its immense potential to transform health care treatment and improve health. We can, however, reduce the risk of genomic data being misused through the adoption of strategies and protective mechanisms that ensure it is handled according to societal and individual values, while at the same time supporting scientific advancement for the benefit of populations. In this policy brief we outline the key policy challenges pertaining to genomics and provide best-practice examples on how they have been addressed by countries in Europe and beyond, which are summarized in the table on pages 8-9.
<table>
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<th>KEY CHALLENGES</th>
<th>EXISTING OR EMERGING SOLUTIONS AND BEST-PRACTICE EXAMPLES</th>
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| Data collection                                    | • Art. 9(2) of the GDPR makes an exemption whereby sensitive data can be processed without going back to obtain explicit consent  
• The FAIR Guiding principles for data management and stewardship: findable, accessible, interoperable, reusable  
• Emergence of new consent models, such as dynamic consent, e.g. UK Biobank uses a three-part model to obtain consent, with ‘legitimate interest’ (GDPR Art. 6) additionally used for lawful processing of data |
| Data storage                                        | • Using centralized or dispersed storage facilities (both have strengths and weaknesses with regard to security challenges); storing data locally, but allowing algorithms to come to the data; using encryption and secure data platforms, such as the Keyless Signature Infrastructure (KSI) blockchain technology in Estonia, to protect sensitive genetic data  
• Providing personnel having access to data with training on cyber security |
| Data interpretation and reporting                  | • Developing guidelines and protocols for performing tests and how to handle the return of results  
• Developing new models and frameworks of genetic counselling  
• Education, training and continuing professional development for clinical geneticists, genetic/genomic counsellors and other health professionals who perform tests and/or provide results, advice and counselling in relation to genomic information |
| Data access, sharing and use for research           | • Establishing greater transparency over data access and sharing by developing comprehensive consent procedures  
• Mechanisms, such as data access oversight bodies, can be put in place to maintain oversight of downstream data uses which are not yet known at the time of data and sample collection |
| Interpretations of what may classify as legitimate use (GDPR Art. 6) of genomic data may vary among data processors | • Developing national and institutional guidelines on ethical and legitimate sharing and use of genomic data, as done by, e.g., Genomics England  
• Cataloguing best practices and developing frameworks for responsible sharing by international organizations, e.g. by the Public Population Project in Genomics and Society, and the Global Alliance for Genomics and Health-Related Data |
| Confidentiality, consent, data protection and human rights should be assured when data is shared across national borders | • Art. 45 of the GDPR restricts personal data sharing with third countries unless adequate data protection procedures are in place, with exceptions for some data controllers or processes with adequate safeguarding processes (Art. 46.1)  
• Developing effective and flexible research governance models that are harmonized across jurisdictions  
• Apply FAIR principles as mentioned above |
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<th>KEY CHALLENGES</th>
<th>EXISTING OR EMERGING SOLUTIONS AND BEST-PRACTICE EXAMPLES</th>
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<td>Data access, sharing and use for clinical purposes</td>
<td>Ensuring that clinicians understand the rules and regulations surrounding data sharing: • Providing special education and training, which can be facilitated by guidelines and codes of practice on confidentiality and data-sharing practices, e.g. principles on Disclosing Data for Secondary Purposes developed by the British Medical Association (BMA)</td>
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<td>Facilitating implementation of genomic medicine into clinical practice</td>
<td>• Developing technical standards and policy guidance, e.g. the framework developed by NHS England in conjunction with Genomics England to commission whole genome sequencing (WGS) for routine care; the France Genomic Medicine Plan 2025 targets the establishment of a generic care pathway to make ‘genomic medicine’ available to all affected patients in the country</td>
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<td>Data access, sharing and use by the private sector</td>
<td>Minimizing concerns over privacy and inappropriate use of data in those who provided it: • Educating patients and the public about the benefits that may result from private involvement in genomic initiatives • Developing procedures to ensure the concerns and values of patients and the public are taken into account, especially in public–private partnerships, e.g. through the establishment of governance boards that include patient or public representatives • Ensuring that private-sector actors adhere to codes of good conduct, have transparent governance and monitoring procedures, and demonstrate the value of their research in terms of benefiting health and health care, e.g. FinnGen project in Finland • Enacting protective legislation, e.g. the United States’ Genetic Information Nondiscrimination Act (GINA); the Code on Genetic Testing and Insurance in the UK; the Biobank Act (2013) and the proposed new genome law in Finland</td>
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<tr>
<td>Minimizing concerns over privacy and inappropriate use of data in those who provided it</td>
<td>• Appropriate use of patents (e.g. on new medicines for a specified time, but not DNA sequences) or use of copyright to protect proprietary databases • The European Patent Convention allows patents awarded by the European Patent Office to be challenged (e.g. successful opposition by various actors against a BRCA1 patent awarded to Myriad) to facilitate data sharing and research • Enforcement of the Unitary Patent (expected at the end of 2020) may necessitate developing more strategic innovation management</td>
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<td>Allowing a reasonably necessary level of intellectual property protection to support private research and development (R&amp;D) efforts, while also protecting the interests of patients and the public</td>
<td>• In the absence of a common legal framework specifically targeting DTC-GT in the EU, some countries regulate data-sharing practices of DTC-GT in national regulations (e.g. a ban in France, Germany, Portugal and Switzerland) • European consumer protection laws and more specific laws on in vitro diagnostic (IVD) medical devices at the EU level affect DTC-GT regulation; national regulation is also influenced by international documents such as the Council of Europe’s internationally binding Convention on Human Rights and Biomedicine. Stronger instruments for enforcement are needed. • A number of DTC-GT companies in the United States have pledged to be more transparent when they share user data</td>
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The EU’s GDPR has major implications for the use of genomic data in Member States and elsewhere

The GDPR, which came into force in May 2018, is a key EU regulation that has significant implications for the use of genomic data in research and clinical practice as it applies to the processing of all personal data. The GDPR sets out the principles for lawful processing of such data (Art. 5) and specifies six legal bases for processing (Art. 6). The GDPR lists genetic data as ‘special categories of personal data’ or sensitive data (Art. 9), which makes their processing subject to the adoption of adequate organizational and technical safeguards, such as pseudonymization. The GDPR has important implications for countries both within and outside of the EU as it protects personal data of all data subjects residing in the EU.

Beyond the GDPR, regulations over the purposes for which genomic data is used and to safeguard public interest are in place in some countries

While the GDPR represents a major regulatory change for genomics, legislative responses at the European level banning discrimination based on genetic data go back to the 1990s, with the adoption of the Oviedo Convention on Human Rights and Biomedicine and the Charter of Fundamental Rights of the European Union. At the national level, many countries have adopted legislation protecting individuals from discrimination on the basis of genomic data by, for example, employers and health insurance companies. Further measures, especially governance structures, are nevertheless needed to ensure that technological and medical advances benefit patients and the public, based on shared values.

Maximizing the benefits of genomic technology requires the full and informed participation of patients and the public

While developing appropriate regulation and/or other governance structures may be challenging, it is, as shown in this policy brief, not impossible and much work in this area has already been undertaken. The major challenge for decision-makers and regulators is, on the one hand, to avoid over-regulating low-risk processing of genetic data, and on the other hand, to ensure security and protection for high-risk processing activities, while at the same time taking into account relevant ethical and social issues as well as specific national values, goals and contexts.

What is also needed to harness the potential of genomics is an active dialogue with all stakeholders, including commercial actors, to build broad patient and societal trust in genomics and the governance of it. Proper engagement and education of patients and the wider public will help place their values and concerns at the centre of genomic initiatives and ensure they are active participants in genomic medicine developments. The goal should be a society where both public and private actors see the added value of genomics and the necessity to collaborate to achieve its full potential on the basis of shared values. In order to maximize the potential of genomic data, it should be linked to other forms of information at the individual and population levels. This in turn depends on effective information and communication technologies combined with established ethical principles and governance procedures for the sharing and use of health data.
1. Introduction: Why this brief?
The word genome refers to the complete genetic make-up of an organism. The first sequencing of the human genome, almost two decades ago in 2003, stimulated a revolution in understanding gene function and expression, presenting us with new opportunities to understand far more about the aetiology of human health and disease, both in individuals and in populations.

Genomics has the potential to improve the health of individuals and populations
Genomic developments have transformed the science of genetics, which once focused largely on single genes and their mutations that give rise to monogenic inherited diseases, such as sickle-cell disease or cystic fibrosis (see Annex A for further details on the difference between genomics and genetics). Technological advances now allow an individual’s whole genome to be analysed rapidly, providing a wealth of information, ranging from insights into one’s ancestry to predicting, with varying degrees of precision, one’s risk of developing some health conditions and diseases. The remarkable pace at which ever more individual genomes are sequenced, with greater speed and lower cost, is providing an explosion in knowledge, offering once unimaginied potential for understanding the aetiology of disease and potential innovations in treatment.

Together with advances in epidemiological research, genomics is also shedding new light on the complex area of gene–environment interactions and genetic and environmental causes of disease, facilitated by public and private biobanks that collate large stores of human biological samples. Simultaneous advances in big (health) data analytics, artificial intelligence (AI) and robotics are transforming our capabilities to handle and analyse this complex data, leading to new knowledge and insights that have immense potential to improve patient and population health. While genomic medicine is still an emerging field and in populations.

Direct access to genomic information by citizens raises ethical and legal challenges
Outside of clinical or research settings, citizens have been able to access their health-related genomic information through commercially available direct-to-consumer genetic testing (DTC-GT) services for more than a decade. Together with the emergence of directly accessible online interpretation services, these offer consumers ever more insights into their genetic characteristics and predispositions towards developing certain diseases. Proponents of DTC-GT argue that it reduces financial and technical barriers to genetic testing and that providing genetic information directly to consumers may lead to improved compliance with advice on healthy behaviours and greater participation in screening (Hogarth & Saukko, 2017). Others contend that the clinical validity of these tests has not yet been established, making their accuracy unknown (Nordgren & Juengst, 2009; Hogarth & Saukko, 2017). Moreover, unless regulated otherwise, direct to consumer testing bypasses the health sector and the involvement of health professionals, which reduces opportunities for counselling if positive results are received.

The rapid progress that has been made in genomics over the past two decades has created much debate (Boccia, 2014). On the one hand, genomics has the potential to deliver earlier diagnosis, more effective prevention programmes and more precise targeting of therapies, in some cases challenging our understanding of the nature of certain diseases. On the other hand, it raises a range of ethical, social and legal challenges. The US National Research Council identified a number of these challenges as early as 1988, prior to the 1990 launch of the Human Genome Project (the international, collaborative research programme to map the entire human genome, completed in 2003). The Ethical, Legal, and Social Implications (ELSI) programme was also founded in 1990 as an integral part of the Human Genome Project. The mission of the ELSI programme was to identify and address issues raised by genomic research that would affect individuals, families and society (Genetics Home Reference, 2019; WHO, 2020). The challenges that were identified related to, among other issues, protection and ownership of data, the need for care in interpreting data, potential misuse of data by commercial organizations, especially insurance companies, and questions about autonomy and the potential for stigma (National Research Council, 1988). As insights from genomics are increasingly used in clinical settings to inform personalized medicine, these ELSI considerations have been broadened, with many concerned this will widen existing inequalities in health care (Brothers & Rothstein, 2015).

This policy brief provides an overview of policy approaches to regulating the processing of genomic information
In this brief, we review some of the ethical, social and legal challenges that must be considered in relation to human genomic research1. We also show examples of selected policy responses that have been adopted across Europe and further afield to address regulatory issues and highlight areas where policy responses are still needed. Our focus is on human genomes, while the issues covered relate primarily to risk profiling and prenatal and neonatal screening rather than somatic gene editing. We show that careful regulation and close and continuing stakeholder engagement will be necessary to address ELSI challenges and to ensure that developments in the genomics field occur on the basis of shared values.

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1 Applications that involve the actual manipulation of the genome (such as gene therapies or genome editing or engineering) are beyond the scope of this brief. Applications that involve non-human subjects (such as pathogens or plants) are also excluded.
In the two accompanying Annexes, we provide additional background material that may be of interest for some readers. Annex A includes an overview of some key definitions pertaining to genomics and considers some of the applications of genomic research in health care that have already been achieved. In Annex B, we explore some key international and national initiatives in genomic research.

2. What are the key ethical, legal and social challenges related to the growing availability and application of human genomic information?

Technological advances are making genotyping and genome sequencing more affordable and accessible, creating new possibilities to improve diagnosis, guide treatment (including better targeted pharmaceutical treatment), and stratify populations according to disease risk (see Annex A for more details on the potential applications of genomics in health care). These developments, along with the growth of DTC-GT by commercial providers, raise important ELSI challenges at the individual level as well as for health systems and society as a whole.

There are concerns that genomic data may be misused in ways that undermine individual privacy and broader societal values

One of the biggest concerns pertaining to ELSI in the genomics field is the potential for genomic data to be used for discriminatory purposes in the absence of regulation, both within and outside of the health sector. For instance, will providers of mortgages, other lenders or employers request information on genetic tests and prevent people with predisposition for developing certain conditions from accessing loans or being offered employment? Will genomic tests be used to prove someone is of ‘pure’ ethnicity? Or will preimplantation genetic testing allow people to select the ‘best’ embryos based on polygenic risk scores (PRS)? There are also some concerns over its use for law enforcement purposes. Will, for example, holders of genomic data be forced to hand over information on DNA to law enforcement agencies to help find people suspected of criminal wrong-doing?

Further, the exceptionally detailed information on individuals that is generated by genomics poses a potential threat to the concept of risk pooling that can be argued to underpin solidarity in European health systems (Council of the European Union, 2006). One way of thinking about European health is that its collective financing represents a form of risk pooling, either through social insurance or taxation: confronted with unknown risks, we pool our risk in order to avoid any individual facing catastrophic expenditure in the event of illness. Genomics, by generating information about future risks, could make risk pooling more difficult to manage. However, in its statement on the underlying values of European health systems, the European Union (EU) talks about risk pooling, but about universality, equity and solidarity (Council of the European Union, 2006). From this perspective, the challenge in relation to more accurate genomic information is to ensure that it is used in ways that reflect those values.

Figure 1: Selected developments in the area of regulating genomics or with relevance to genomics in Europe, 2000–2019

- **European Union**
  - Human genome sequenced
  - Additional protocols to the Council of Europe Convention for the Protection of human rights and human dignity in the field of biology and medicine on biomedical research adopted (2005), in force (2007) and on genetic testing for health purposes (2008)
  - Council of the European Union adopts conclusions on personalized medicine for patients
  - Council of Europe adopts recommendations on research on human biological material
  - EU General Data Protection Regulation (GDPR) adopted
  - Council of Europe adopts general recommendations on guidelines for the Protection of human Big Data processing
  - Regulation (EU) 2017/746 on in vitro diagnostic medical devices comes into force
  - GDPR enforced
  - 12 EU Member States sign a declaration towards access to at least 1 million sequenced genomes in the EU by 2022
  - Additional Protocol to the Oviedo Convention on Genetic testing for Health Purposes, comes into force

- **International/global**
  - UNESCO adopts the Universal Declaration on the Human Genome and Human Rights (1997)
  - International Declaration on Human Genetic Data (2003)
  - International Declaration on Bioethics and Human Rights (2005)
  - UN Convention on the Rights of Persons with Disabilities
  - International Cancer Genome Consortium established
  - Revision of the 1964 Helsinki Declaration of the World Medical Association (WMA) concerning the use of human tissues or information in medical research
  - Global Alliance for Genomics and Health (GA4GH) established
  - WMA draws up the Taipei Declaration on health-related biobanks

Source: Authors
Appropriate regulation can help realise the potential of genomics while protecting individuals and societies.

Ultimately, the existence of new knowledge brought about by genomic advances should be embraced as it holds potential, if not yet fully realized, to improve health treatments. Reducing the risk of genomic data being misused by developing strategies and protective legal and regulatory mechanisms to handle it according to our values, while at the same time ensuring the support of scientific advancement to the benefit of our populations, should remain the goals of policy-makers. These dual aims can be achieved by careful regulation of the processing of genomic data and engaging and educating patients and the wider public to become active participants in genomic medicine developments. Many regulatory instruments, protocols and other strategies have already been launched at the international and European levels over the past two decades to balance these dual aims (see Figure 1 on previous page). Some of these key initiatives are explored in greater detail in the subsequent sections.

The particularities of genomic information make developing regulation challenging.

It is important to note, however, that developing such strategies and instruments can be particularly challenging. This is because genomic data, in almost all cases, is personal, sensitive data, and its potential use extends far beyond enabling better treatment for the individual who provided it. One way of considering the challenges presented by genomics is in terms of its potential to generate information that is distant from the immediate diagnosis and treatment of an individual patient. We can identify several types of distance, which we summarize in Figure 2.

Of course, none of the challenges outlined in Figure 2 are exclusive to genomic data. It has long been possible for investigation of one current condition to generate information about another condition now or in the future, or to diagnose conditions for which there is no effective intervention. This is, for example, the case with incidental findings of body scans, where people are given a copy of their medical images and are encouraged to get second opinions, which can create additional health care burden.

Figure 2: Challenges presented by genomic information described as various types of ‘distance’
Genomics may, however, add substantial scale to these issues due to the large amount and scope of information that genomics produces. Further, we typically perceive genetic data to be a particularly powerful type of information, and that gives rise to higher expectations about the impact of such data – and, in consequence, greater concerns. Thus, addressing these ethical, legal and social issues requires considering the particular issues that genomics raises in relation to the overall goals and values of health systems.

3. What are the key regulatory challenges related to the processing of genomic data and how have these been addressed?

The processing of genomic data covers a number of areas from data collection, storage, alteration, retrieval, use, disclosure or dissemination, reinterpretation, and erasure and destruction, among others. In the sections below we outline the key challenges pertaining to various processing operations and provide best-practice examples on how these challenges have been addressed by countries in Europe and, where relevant, beyond. We start first by outlining the EU's General Data Protection Regulation, which represents a major regulatory change with substantial implications for the processing of genomic data.

The General Data Protection Regulation

GDPR is the most important regulation affecting the processing of genomic data at the EU level

The EU’s General Data Protection Regulation (GDPR) is an important regulatory change at the EU level that has significant implications for the processing of genomic data in research and clinical practice. The regulation applies to the processing of data of EU citizens and residents for professional or commercial activity, irrespective of the location of the data processor, meaning it has implications for organizations and companies outside of the EU. The regulation came into force on 25 May 2018, replacing the EU’s previous legal framework that dates back to 1995 (Directive 95/46/EC) and introduced a number of new obligations that EU Member States must comply with (see Box 1). At the same time, it creates space for Member States to decide how to implement the GDPR at the national level, which may threaten harmonization of the rules governing research and translation of research into clinical practice (Mondschein & Monda, 2018).

According to Articles 4(2) and (6) of the GDPR, data processing covers ‘a wide range of operations performed on personal data, including by manual or automated means. It includes the collection, recording, organization, structuring, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, restriction, erasure or destruction of personal data’ (European Commission, 2020).

GDPR treats genomic information as personal sensitive data

Human genetic data is sensitive by nature. Recital 51 of the GDPR designates personal data which is, by its nature, particularly sensitive in relation to fundamental rights and freedoms as requiring specific protection, as the context of its processing could create significant risks to those fundamental rights and freedoms. Such personal data should not be processed unless it falls within one of the specific provisions set out in the GDPR (see Box 1). Member States may also establish their own specific provisions on...
When can genomic data be considered as anonymous?

The unique nature of genomic data poses challenges for its anonymization (opinion DNO 3744/41/2016 of the European Data Protection Supervisor (EDPS)). Key for determining the likelihood of identification are the peculiar characteristics of specific genetic datasets as well as contextual factors, such as the institutional setting in which processing occurs, the stage of processing, the availability of cross-referenceable datasets, and incentives and availability of resources for reidentification (Shabani & Marelli, 2019). For any given dataset, de-identifiability of genetic data should be regarded as a dynamic exercise: it cannot be achieved once and for all, and should be periodically reassessed (Shabani & Marelli, 2019).

Data on genomic variations cannot in most cases be linked back to an individual and is not subject to the same restrictions, unless non-identifiability cannot be ascertained. It can therefore be shared and processed with fewer constraints, making it a powerful data source for both research and health care. However, while sharing of non-personal (anonymous) data creates fewer legal considerations, it still raises legal and ethical concerns, as identifiability may not always be excluded. Further, circulation of such anonymous data via open-access databases may increase the likelihood of re-identification of de-anonymized datasets. As a result, data controllers* may consider genomic datasets as always identifiable, with consequences for research and clinical use (Shabani & Marelli, 2019).

Processing of personal data under the GDPR

There are expectations, as specified by the GDPR, that genomic data will only be shared, where necessary, for specified, explicit and legitimate purposes (see below). Interpretations of what may classify as legitimate use of genomic data vary between potential data processors*, making it important that national regulation and guidelines on ethical and legitimate sharing of genomic data are developed to ensure that data is only shared when appropriate and under circumstances likely to bring benefits to patients and the wider public.

Article 5 of the GDPR sets out the principles for lawful processing of personal data. These principles are:

- **Lawfulness, fairness and transparency:** processing of personal data is lawful when it is based on one of the six legal bases listed in Article 6 GDPR, which are: (1) consent; (2) performance of a contract; (3) legal obligation (not including contractual obligations); (4) vital interest of the data subject; (5) performance of a task carried out in the public interest (e.g. the "1+ Million Genomes" project) or in the exercise of official authority vested in the controller*; (6) legitimate interest of the controller or by a third party. The principles of fairness and transparency relate to the fact that data subjects must be informed in a comprehensive manner about the purpose and scope of the processing as laid down in Articles 12–14 GDPR.

- **Purpose limitation:** in line with the principle of transparency, data can only be processed for a specific purpose, which has to be communicated to the data subject. In the context of research, Article 89 GDPR provides for certain derogations if the requirements under that article are fulfilled, allowing for further processing (see more below).

- **Data minimization:** this principle requires controllers to minimize the data they collect and keep.

- **Accuracy:** the controller is obliged to ensure the accuracy of the data.

- **Storage limitation:** this principle requires controllers to specify the time limit after which data will be deleted. In the context of research, Article 89 GDPR provides for certain derogations if the requirements under that article are fulfilled.

- **Integrity and confidentiality:** this principle requires that the integrity and confidentiality of personal data are ensured. It links with the obligations of data security, having in place adequate technical and organizational measures as well as the requirement to report data breaches to the supervisory authority and/or data subjects under certain circumstances as specified in Articles 33–34 GDPR.

If special category data such as genetic data is processed, one needs to identify both a lawful basis for processing (i.e. Article 6 of the GDPR) and a special category condition for processing in compliance with Article 9(2); these do not necessarily have to be linked.

The conditions for processing special category data listed in Article 9(2) are: explicit consent; employment, social security and social protection (if authorized by EU or Member State law); vital interests; not-for-profit bodies; made public by the data subject; legal claims or judicial acts; reasons of substantial public interest (with a basis in EU or Member State law); health or social care (with a basis in EU or Member State law); public health (with a basis in EU or Member State law); archiving, research and statistics (with a basis in EU or Member State law).

The provisions of the GDPR do not apply to the processing of genomic data of deceased and unborn people. It should be noted, however, that genomic data is shared by past and future generations of deceased and unborn people, which is why the rights of living relatives can be violated by processing data produced from samples of people already dead. The fact that genetic data is shared by families adds to the challenge as one person’s genome data can allow for the identification of another person. This is a rapidly moving field and there are concerns that existing legislation, including the GDPR, may not have fully recognized all the implications (Shabani & Marelli, 2019).

*Under the GDPR, the controller is the entity which decides on the purpose and the means of the processing; the processor is the entity that processes the data on behalf of the controller.

Data collection

Data collection is usually based on consent but the GDPR allows exemptions

Genomic data is produced by a variety of entities, including public and private biobanks, health care providers and private DTC-GT companies, with data often stored in different datasets and formats. Collection of human biological samples, from which genomic data is derived, is generally based on consent (Box 2), usually paper-based or electronic at the point of sample collection. However, new consent models, such as dynamic consent, have been emerging to accommodate the special issues that arise with the further processing of genomic data and emergence of its new applications. Allowing consent to change over time can
help to build trust in participating in genomic initiatives as people know that they can change their minds about the use of their data at a later stage.

**Biobanks have been developing innovative models of consent**

Biobanks, which collect and store blood cells or other tissues, genetic or proteomic information that may have direct implications for the individual donor, have devoted considerable attention to developing comprehensive consent procedures for the collection of human biological samples. The UK Biobank, for instance, uses a three-part model to obtain consent (see section on data access, sharing and use for secondary purposes). Because of the health-related nature of the personal information that individuals have provided to the UK Biobank, ‘legitimate interest’ is additionally being used as a valid reason for lawful processing of data (see Box 2).

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**Box 2: Genomics and the issue of consent in the era of the GDPR**

Informed consent is a cornerstone of biomedical ethics. The aim of consent has traditionally been to ensure that only ethically sound medical research is carried out and that the research subject is protected from harm. Consent is required, for example, to take a sample and subsequently to process the data derived from it. The form of consent varies depending on the context and purpose for which consent is given.

The situation is complicated by the introduction of the EU GDPR. Under the GDPR, consent does not always have primacy when regulating the use of genomic data for research or clinical purposes. Article 6(1) of the GDPR establishes six lawful reasons for processing personal data, of which consent is only one (see Box 1). If special categories of (sensitive) personal data, such as genetic data, are to be processed, one of the conditions in Article 9(2) must be applied. While explicit consent is one of the options provided by Article 9(2), it is not always the most appropriate option, even if separate legal or ethical norms (relating to e.g. research) require consent for a medical intervention such as taking a sample.

Notably, Article 9(2) makes an exemption whereby sensitive data can be processed including, ‘archiving purposes in the public interest, scientific or historical research purposes, or statistical purposes’, without going back to obtain explicit consent of research participants. According to Article 89, this can only occur in cases where secondary processing and data sharing is ‘for reasons of substantial public interest’ (e.g. the use of newborn bloodspots to monitor the prevalence of HIV infection in women giving birth (Peckham et al., 1990), under conditions where ‘suitable safeguards’ are developed to protect anonymity where possible and to ensure security of data and to comply with laws and regulations in individual Member States.

Correspondingly, Article 9(2) allows sensitive data to be processed for the purposes of, for example, preventive medicine, medical diagnosis, provision of medical treatment or management of healthcare services on the basis of law and subject to appropriate conditions and safeguards. Explicit consent is therefore one way to legitimize processing of genetic data within the EU, but not the only way if it is being carried out for reasons in the public interest, such as for research or clinical purposes. Using consent has many benefits as it means that individuals have a genuine choice and ongoing control over how their data is being used. However, using consent as a legitimate basis for processing is not always an option for the data controller*, if the legal basis for processing is based on national legislation, as has been described above. Nevertheless, adherence to the GDPR ensures that processing is transparent and the data controller is accountable. It also puts people’s rights and freedoms at the centre and helps build confidence and trust.

*Under the GDPR, the controller is the entity which decides on the purpose and the means of the processing.

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**Data storage**

A single human genome takes up 100 gigabytes of storage space. Storing increasing amounts of genomic data will thus require unprecedented storage capacities, with development of new storage technologies. Some researchers anticipate the creation of genomics archives for storing millions of sequenced genomes. Others believe that cloud computing is the best storage model to provide the capacity needed for DNA sequencing (Costa, 2012). Yet, given how the price of genomic technology is expected to fall, regeneration of genomic data whenever the need arises may be more cost-effective than long-term storage, which can be very costly and prone to technical challenges of data retrieval and integrity. Even now in clinical genetics, due to legal requirements DNA is often stored and reanalysed at a future time for a specific question.

**Long-term storage of genomic data necessitates high-quality curation of data archives**

A further technical consideration for data storage is that genomic data must be stored for long periods of time, given that genomic data has relevance not only for an individual but also for historical monitoring of population risk, potentially over several generations. Further, only by maintaining a long-term genomic database can incorrect and obsolete data be deleted and replaced with new and, hopefully, more accurate interpretations. If incorrect or outdated genomic data is stored, erroneous conclusions may harm individuals. Consequently, there is a need for very high-quality documentation and standards of curation of data archives, recognizing that legacy data may have been produced with obsolete technologies or in unaccredited laboratories.

**Ensuring data privacy and security requires robust infrastructure, training, as well as careful regulation of access**

Beyond technical difficulties involved in data storage, the key regulatory challenge is ensuring privacy and security. Genomic data is no different from other health-related data in being at risk from data breaches and cyber-attacks that may lead to data being stolen and sold, deleted or corrupted. This not only violates individual privacy but has the potential to cause direct harm. To counter this, data can be stored in centralized or dispersed facilities. Both have strengths and weaknesses with regard to security challenges and both alternatives are, in principle, subject to similar risks. Legal issues that must be addressed include how and to whom legal access of the stored data is given, for which purposes and to what extent. For example, can the data be used off-site or only in on-site safe havens?
Platforms that host or analyse genomic data need to be protected against security threats, including cyber-attacks. Attention should be paid not just to the development of a secure computing platform but also to the security of any actual or potentially associated cloud providers, taking account of legal protections that cloud services enjoy in their respective jurisdictions, while ensuring secure, controlled modes of access (Bentzen & Svantesson, 2017). Almost all private companies and public initiatives, such as biobanks that undertake genetic testing, now use encryption and secure data platforms, such as the Keyless Signature Infrastructure (KSI) blockchain technology in Estonia, to protect sensitive genetic data.

Robust digital infrastructure is vital for cyber resilience, but is not sufficient on its own. A large proportion of data breaches in the health sector is due to employee behaviours, such as covertly abusing data access or clicking on infected email links. Training on cyber security and other measures to mitigate security risks are therefore crucial. Strong oversight and regulatory frameworks, with in-built monitoring, evaluation and accountability processes are also essential (Williams & Fahy, 2019).

Data interpretation and reporting

Before the genomic era, genetic testing was used for diagnosis of certain genetic conditions by testing a single or small number of genes. Once it became possible to sequence the entire genome, the volume of data available to researchers, clinicians and individuals (via DTC-GT) on the genetic determinants of health and disease increased exponentially. However, many variants in genes have no known function or are of uncertain (or unknown) significance (VUS) and there is uncertainty about how to deal with incidental findings unrelated to the clinical indication of the test. This is especially complicated when the variants relate to late-onset or untreatable conditions. As noted, this is not unique to genomics and is equally true of many other techniques that can generate incidental findings, such as magnetic resonance imaging (MRI) testing. What is distinct about genomics is that each year the knowledge base improves regarding the interpretation of VUS, so new diagnoses and research discoveries will frequently be made on data collected in previous years. Genomics also amplifies complications due to the scale and scope of information collected and implications for family members (Borry et al., 2018).

Reporting of genomic data to individuals may require balancing of ethical and legal considerations

It is sometimes recommended that results which lack clinical utility or actionability, or have uncertain medical or reproductive significance, are not returned to participants for fear they may cause undue anxiety (National Academies of Sciences, Engineering, and Medicine, et al., 2018). On the other hand, it is sometimes argued that banning the return of non-clinically significant results advances the popular view that the human genome has only one true medical meaning. There is an emerging view that genomic data instead may have personal utility or non-medical meaning in the form of entertainment to people even when it is not actionable (Thorogood, Dalpé & Knoppers, 2019). According to this view, discussing genomic data lacking medical significance should not be seen as the practice of medicine but rather of genetic science.

Importantly, there is growing pressure to make all personal data available to an individual, as this is increasingly recognized as a fundamental human right, and withholding relevant information from patients could be deemed unethical. Nonetheless, while studies have found that patients want to receive information about the condition they were tested for, patient support for returning incidental findings was more mixed, with many concerned over the potential for information to be used for discriminatory purposes (Tabor et al., 2011, 2012). Overall, however, patients are consistent in stating that their preferences in terms of wanting to receive or not receive information should be respected and that consent procedures should be in place to allow them to change their mind at any time (Tabor et al., 2011, 2012). Many international laws and policies therefore require researchers to provide information on a project’s policy on the return of results as part of the consent process (Thorogood, Dalpé & Knoppers, 2019).

It is noteworthy that ethical justifications and legal justifications are two different things. Even if restricting reporting of results is ethically justified, it may not be constitutional to enact restrictions into law. Regulators have to make a decision on whether they want to enable or restrict reporting or alternatively set conditions. Currently, governance instruments and guidelines including the GDPR and OECD Guidelines on Human Biobanks and Genetic Research Databases (OECD, 2009) do not mandate feedback of results to patients or participants in research. Nevertheless, they do state that processors of genetic data should have procedures and principles in place governing feedback to participants. The Oviedo Convention is also explicit in stating that people are ‘entitled to know any information collected about his or her health’ (Council of the European Union, 1997).

Reporting guidelines and protocols have been developed but require elaboration and harmonization

Different guidelines and protocols that describe how to handle the return of results, including VUS and incidental findings, have been developed but need further elaboration as well as potential harmonization, especially with regard to the pertinent responsibilities of involved parties (Borry et al., 2018). Opinions regarding the proper way of reporting results will of course vary according to context and the parties involved (Evans, 2014). For example, in a research context, a research participant may request the results of genomic testing and the investigator may be willing to share the results but is concerned that doing so may violate regulations. It is therefore important that any researcher, health professional or other involved party who may be tasked with communicating results of genomic testing is provided with guidelines and codes of conduct as to when and under what circumstances this sensitive information may or should be shared. In a review of policy documents,
Thorogood, Dalpé & Knoppers (2019) identified several general principles that have been developed to guide the return of results that take into account participants’ preferences over whether to know or not know certain findings:

1. The rights and interests of participants take precedence over the goals of research to generate new knowledge.
2. Researchers have some level of responsibility for the welfare of participants, and are responsible for their protection and for mitigating the risks of their participation in research.
3. Consent to research is informed, voluntary, and ongoing.
4. Participants have a right to know information relevant to their health. The wishes of participants not to know health information, however, are also to be respected.
5. Participants’ privacy and the confidentiality of their identifiable information should be protected.
6. Research policies on the return of results should be informed by participant and community engagement.
7. Researchers have a duty to share general results of research with the public and with participants.

As noted, genomics is a fast-evolving field and outcomes that are non-significant now may be reinterpreted as clinically significant in the future as new knowledge is uncovered. Informing patients about the potential of reinterpretation of results in the future is very important, to ensure that patients can make informed decisions on whether they would like to receive this information and under which circumstances. When applicable, the process of recontacting patients necessitates the involvement of health professionals and there are important concerns about the feasibility of doing so in health care settings, especially given constraints on health care resources and the costs involved, as well as legal and ethical considerations over privacy and duty of care (Carrieri et al., 2019). For actors involved in interpreting data and reporting results, it is therefore important that systematic procedures are put in place to ensure that any updated findings and information are communicated to all affected patients in an appropriate and timely manner. This raises questions over how and how frequently to update and consult reference databases to reinterpret results based on emerging knowledge and who is responsible for following up VUS after a test has been conducted (Bilkey et al., 2019a).

National guidance and tools to facilitate recontacting are currently scarce. However, the European Society of Human Genetics (ESHG), in collaboration with research groups from various countries and following public consultation, has developed recommendations on recontacting patients with new and clinically significant results from past genetic testing. Among 13 recommendations in total, the ESHG suggests that: recontacting should take place for findings with clinical or established personal utility, even though there is currently no duty to do so; the decision to recontact should be based on the best interests of the patient/family; recontacting should be sustainable for the health care system and its workforce; and recontacting should be a shared responsibility with the patient (Carrieri et al., 2019).

The development of decision support systems and other tools to assist in the interpretation of data must feature strongly in future collaborative efforts if genomic data is to be used effectively in health care. Currently, the interpretation of genomic variation requires specially trained personnel but considerable work is already being done worldwide to automate this process (Rees, 2019).

**New models and frameworks for genetic counselling need to be developed**

It is also important that genetic counselling policies should be developed in relation to the different ways individuals can access genomic information. As part of this, it is important to (re)define the roles of clinical geneticists, genetic/genomic counsellors and other professionals, such as general practitioners (GPs) specialized in clinical genetics who provide advice in relation to the wide array of genomic information. Enhanced technical options for genetic testing are not yet accompanied by comprehensive genetic counselling models for the genomic era. New models and frameworks of genetic counselling that extend beyond the traditional clinical genetics and genetic counselling setting need to be developed, perhaps facilitated by digital health solutions, such as online consultations and patient portals. Given the potential of new sequencing technologies to generate high volumes of data, and uncertainties around results of the data generated, there is a pressing need to revitalize current genetic counselling services and also to enhance awareness and training of all health professionals who may interact with those providing these services, to help them understand when patients and their families should be referred.

**Sequencing institutions need policies and procedures in place to guide the return of findings**

Once, most patients followed a specific pathway through the health care system to access their genetic information (via clinical geneticists and/or genetic counsellors) on the basis of specific clinical concerns or family history. They now have the opportunity to obtain genetic testing without the intermediary of a professional assessment of clinical need and can obtain testing for a variety of purposes, including mere curiosity. Individuals may also choose to use sequencing services that provide access to raw data without interpretation, providing them with ‘unfiltered’ genetic information to use as they see fit. They could, for example, attempt to ‘self-interpret’ with the support of publicly available sites for the analysis of genetic data. It is therefore important that sequencing institutions have transparent policies and procedures for raw genomic data access and returning policies (Shabani, Vears & Borry, 2018; Narayanasamy, 2020). In Australia, the National Health and Medical Research Council has developed a National Statement on Ethical Conduct in Human Research, which provides guidance on communication of research findings or...
results to participants (National Health and Medical Research Council, Australian Research Council & Universities Australia, 2007, updated 2018). While the statement requires researchers to have a system in place to guide the return of findings with health significance to participants, it does not expect researchers to return raw genomic data.

Data access, sharing and use for secondary purposes

To capture the full benefits of genomic data, it must be shared with multiple actors, including: researchers to support academic and clinical research; health providers to support delivery of health services and public health activities; and commercial organizations involved in developing and implementing new health technologies or delivering health care services (Figure 4). Data sharing to facilitate greater genomic research and translation of findings into clinical use relies on the implementation of advanced technological solutions, health workers with the right skills and training to contribute to implementation, the active involvement of citizens and patients that support translation, and implementation of strong regulatory and governance procedures (Raza & Hall, 2017).

According to the Bermuda Principles for DNA sequence data sharing developed in 1996, all genomic data was initially meant to be made freely available in the public domain in order to facilitate research and development (R&D) that would benefit society at a faster rate than would otherwise be possible (Jones, Ankeny & Cook-Deegan, 2018). Although this idea is still alive, it is no longer the case in EU Member States following implementation of the GDPR, which classifies genomic data as sensitive personal data (Box 1). Under certain circumstances genomic data may be processed without informed consent

This creates specific difficulties for genomic data that may not be encountered by other forms of health data, as true anonymization may be difficult to achieve or not be practical or desirable for certain types of research. In recognition that these restrictions on their own would inhibit beneficial genomic and other health research, the GDPR (Article 9(2)) identifies specific circumstances under which these regulations may be bypassed, and explicit informed consent is not needed for data processed for research or clinical purposes. For instance, under this scientific exemption, pseudonymized genomic data can be processed for further purposes without explicit consent being obtained, provided it is stored within a controlled network that can only be accessed by approved users and with appropriate safeguarding procedures in place. Well-known existing public databases that operate according to these principles include ClinVar and DECIPHER (Johnson et al., 2019). Secondary processing of genomic data must nevertheless comply with laws and regulations in individual Member States and other EU regulations governing data access, sharing and processing, including those specified by the GDPR (see Box 1).

It is also important to note that, while anonymizing genomic data is a complex task, it remains feasible and many genomic initiatives, such as the 100,000 Genomes Project in the UK and FinnGen in Finland, already take steps to remove personally identifying information from genomic profiles to protect privacy and facilitate secondary use.

Genomic data should only be shared for specified, explicit and legitimate purposes

Of course, while the sharing and secondary processing of anonymized data is not subject to the same legal restrictions as sharing identifiable data, it still raises ethical concerns over appropriate use. There are expectations as specified by

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Figure 4: Primary and secondary applications of genomic data

<table>
<thead>
<tr>
<th>RESEARCH APPLICATIONS</th>
<th>CLINICAL APPLICATIONS</th>
<th>COMMERCIAL APPLICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary use</strong>: producing and using genomic data in a research protocol</td>
<td><strong>Primary use</strong>: prevention, diagnostics and treatment of disease in a single patient</td>
<td><strong>Primary use</strong>: development of new technologies for diagnosis and treatment</td>
</tr>
<tr>
<td><strong>Secondary use</strong>: using data produced in a research protocol for health care purposes (integrating research into clinical practice)</td>
<td><strong>Secondary use</strong>: using existing genomic patient data for the benefit of another patient; using existing genomic patient data for research purposes</td>
<td><strong>Secondary use</strong>: exploitation of the data generated for other purposes</td>
</tr>
</tbody>
</table>

Source: Authors
the GDPR that sensitive data will only be shared for specified, explicit and legitimate purposes, but interpretations of what may classify as legitimate use of genomic data may vary between potential data processors. This makes it important that national and institutional guidelines on ethical and legitimate sharing and use of genomic data are developed to ensure it is only shared and accessed when appropriate and under circumstances likely to bring benefits to patients and the wider public (Williams & Fahy, 2019). While not just applicable to genomic medicine, five key features that a data-sharing initiative designed to deliver public benefits should demonstrate have been elaborated by Involve, Understanding Patient Data and the Carnegie UK Trust (Box 3).

Box 3: Five key features that a data-sharing initiative designed to deliver public benefits should demonstrate
1. Enables high-quality service delivery which produces better outcomes for people, enhancing their wellbeing.
2. Delivers positive outcomes for the wider public, not just individuals.
3. Uses data in ways that respect the individual, not just in the method of sharing but also in principle.
4. Represents, and supports, the effective use of public resources (money, time, staff) to enable the delivery of what people need/want from public services.
5. Benefits that are tangible, recognized and valued by service providers and the wider public.
Source: Scott et al., 2018.

Data access, sharing and use for research

Data access oversight bodies can help ensure appropriate sharing of data for research

Alongside establishing comprehensive consent procedures where appropriate (see above), other mechanisms can be put in place to establish greater transparency over data sharing and access that enhance involvement of research participants (Kaye et al., 2018). Data access oversight bodies are examples of new governance tools that might be able to ensure appropriate monitoring of secondary research uses of data, including downstream data uses which are not yet known at the time of data and sample collection (Shabani et al., 2015). It is expected that oversight bodies can play a key part in ensuring that this data is in safe hands and used in ways that benefit science and society, or are consistent with the consent that has been given. In doing so, oversight bodies should adopt fair, objective and transparent access arrangements (Borry et al., 2018). Oversight bodies should contain representatives from patient and public advisory groups to ensure that the concerns and values of participants and other potential beneficiaries are taken into account. This process will help place patients and the public at the centre of genomic research, so the process takes place with them rather than just to them.

Frameworks are being developed to responsibly share data across borders

In regulating data sharing for research, it is important to recognize that many research initiatives these days are multistited, international (e.g. research consortia) and organizationally complex (Kaye & Hawkins, 2014). Effective and flexible research governance models that are harmonized across jurisdictions are required to meet the needs of current research approaches. However, the regulatory landscape surrounding the sharing of patient data across borders is complex, multilayered and ambiguous, as current models of research governance were created at a time when research was often conducted on one site, by one team and involved a limited number of participants. Responsible data sharing across borders requires appropriate legal frameworks covering confidentiality, consent, data protection and human rights. International organizations such as the Public Population Project in Genomics and Society and the Global Alliance for Genomics and Health-Related Data are helping to address these issues by cataloguing best practices and developing a framework for responsible sharing (Global Alliance for Genomics and Health, 2014).

Data access, sharing and use in clinical settings

Clinicians, health facilities and laboratories are becoming important sources for obtaining, storing and using genetic data. Facilitating data sharing between these entities is critical to support proper use of data for more accurate and timely diagnoses that may otherwise not be achieved by facilities working in silo. In addition, data sharing with public genomic datasets is important to support advancement of knowledge in the field. However, this raises the significant question of whether legal and ethical principles of clinical care or those of research should govern data sharing and access (Johnson et al., 2019).

Some argue that data sharing for clinical uses should not always be based on patient consent

Data sharing that complies with the principles of clinical care generally relies on obtaining the necessary patient consent, which can result in delays and present a major obstacle to data sharing in clinical settings. As such, the principles of data access, sharing and processing followed by research, and as regulated by the GDPR, may be preferred. In addition, many argue that the processing of clinical variants is absolutely necessary for clinical purposes and therefore should not be dependent on the explicit and specific consent of the patient, provided standards and safeguarding procedures are met (Johnson et al., 2019). Further, some have argued that patients that benefit from genome sequencing have a moral and ethical duty to share their data in the spirit of reciprocity and fairness to support advances in health care that may benefit society more widely (Johnson et al., 2019).

Clinicians need to have a good understanding on when data can be shared

The sharing of sensitive patient data collected in clinical settings for secondary use is allowed by law under the GDPR Article 9(2). In many circumstances, this relies on clinicians understanding the rules and regulations surrounding data sharing, which requires the provision of special education and training. Helping clinicians to understand under what circumstances data sharing may be appropriate or encouraged can also be facilitated by putting in place guidelines and codes of practice on confidentiality and data-sharing practices. In the

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UK, for instance, the British Medical Association (BMA) has developed principles on Disclosing Data for Secondary Purposes, which aim to assist Local Medical Committees and primary care GPs in determining how to respond to secondary data access requests for patient data (BMA, 2016).

Countries have put in place frameworks and plans to support implementation of genomic medicine

Developing technical standards and policy guidance to support implementation of genomic medicine in clinical practice is also essential. One example can be found in the framework developed by NHS England in conjunction with Genomics England to commission whole genome sequencing (WGS) for routine care. This framework provides an early example of integrating the clinical evidence base with operational and financial considerations and developing local arrangements for clinical and laboratory genomics infrastructures (Box 4). Similarly, in France, the France Genomic Medicine Plan 2025 [Plan France Médecine Génomique 2025] proposes a transformative, 10-year plan that targets the establishment of a generic care pathway to make ‘genomic medicine available to all affected patients in the country’ (Aviesan, 2016). The French plan also specifies an action to create a research programme to study the economic aspects and implications of integrating genomic medicine into medical practice.

Box 4: Translating genomics into health care in the UK

Genomics England was established in 2013 with £300m government funding to sequence 100,000 genomes from National Health Service (NHS) patients affected by a rare disease or cancer, and their families. This target was met in December 2018. NHS England established 13 NHS Genomic Medicine Centres to support delivery of the 100,000 Genomes Project. Collaboration between a range of organizations and sectors has led to the development of a UK genomics industry.

Patients donate their samples and information using models of informed consent which have been approved by an independent NHS ethics committee. The Genomics England data centre is a secure facility located within the NHS firewall, in which the genomic data and other data relating to the patients are stored, and there are clearly defined policies regarding data access and data sharing.

Combining genomic sequence data with medical records has created a valuable resource, and researchers are currently studying how best to use genomics in health care and to interpret the data to help patients. Genomic data are available to researchers, clinicians and industry through the Genomics England Clinical Interpretation Partnership (GeCIP).

The NHS Genomic Medicine Service was launched in October 2018 to prepare the NHS to implement genomic technologies to provide consistent and equitable access to genomic medicine. It includes a mandated test directory linking WGS for defined rare diseases and cancers to reimbursement; this assures commissioners and health care professionals that the new tests are appropriate for free. The content is developed by following a detailed methodology for evaluation and is updated annually.


Data access, sharing and use by the private sector

Private sector has been critical in facilitating genomic advances

Private companies are heavily involved in collecting, analysing and interpreting genomic data. Partnerships between private companies, research institutions and health care providers facilitate greater investment, new ideas and applications to support genomic research and its use in clinical practice that may otherwise not be possible. For instance, data collected through commercial DTC-GT services have been used to support research into numerous noncommunicable diseases (NCDs), such as Parkinson’s and Alzheimer’s. Pharmaceutical companies meanwhile have part-funded many genomic initiatives, such as the FinnGen study in Finland (FinnGen, 2019), and have used genomic data to support research on drug development and drug responsiveness. Many technology start-ups have also developed advanced hardware and software, including artificially intelligent machine learning systems that can facilitate faster analysis, diagnosis and translation of research findings into clinical practice. In the future, commercial parties are likely to play a key role in developing and marketing personalized drug treatments. The same is true for Conformité Européenne (CE)-approved in vitro diagnostic (IVD) tests that might determine who should be treated or not.

People may have concerns about the use of their data by the private sector

The fact that many innovations, technologies and new drugs that are developed using genomic data are developed by private companies and not by universities or hospitals makes the involvement of private companies in genomic research essential, and very often requires these companies to access publicly owned genomics databases. Yet, people may be less willing for their genomic information to be used in research if private companies are involved, due to concerns over privacy and the use to which their data may be put, especially if it is used to generate financial profit for these companies that may not benefit society. This concern may be heightened if companies sell innovative medicines or technologies that are developed on the basis of analysing genomic data at prices that are unaffordable for some health systems.

Research into public attitudes to commercial access to health data in the UK illustrates this dilemma (Ipsos MORI, 2016). This research found four ‘key tests’ that citizens applied (Figure 5). First, whether the use of data was for a clear public benefit. Second, whether the actors involved were trusted to be acting in the public interest. Third, how anonymized or aggregated the data concerned was. And fourth, effective safeguarding of the data. Genomic information was seen as particularly sensitive, precisely because the potential uses of the data in the future were so unpredictable.
Private companies need to take steps to build public trust about their involvement in genomic initiatives

Each of these ‘key tests’ suggests potential policy responses. One option is better communication and information. For instance, to help alleviate these concerns and build trust in data sharing with private companies, it is important that patients and the public are educated on the huge benefits that may result from genomic research, and the potential contribution of private involvement in genomic initiatives to the public good and to benefiting health and health care. At the same time, private companies should talk to and collaborate with other stakeholders, including patients and the wider public, to ensure the values and concerns that people have surrounding the use of their personal data are reflected in genomic initiatives. In addition, it should be ensured that private-sector actors adhere to codes of good conduct, have transparent governance and monitoring procedures, and demonstrate the value of their research in terms of benefiting health and health care, in order to increase trust in private actors acting in the public interest. The example of the FinnGen project in Finland highlights both the benefits of and good practice in involving private companies in genomic research (Box 5).

**Box 5: FinnGen study as an example of good practice in public–private partnership**

The FinnGen study is a research project aimed at improving human health through genetic research that combines genome information with digital health care data from national health registers. The study plans to utilize 500,000 unique samples collected by a nationwide network of Finnish biobanks, with almost all biobanks in the country participating. It was launched in Finland in late 2017 and is expected to run for 10 years.

The study has four main aims:

1. Produce medical innovations by combining health registry and genome data.
2. Support Finland to become a pioneer in biomedicine and personalized health care.
3. Create a cooperation model between the public sector and health care industry.
4. Provide early access to new personalized treatments and health innovations for all Finns.

FinnGen is a collaborative project, bringing together Finnish universities, hospitals and hospital districts, THL, biobanks and international pharmaceutical companies (Figure 6). The study is funded by Business Finland (a public funding agency for research funding in Finland, directed by the Finnish Ministry of Employment and the Economy) and nine international pharmaceutical companies: Abbvie, AstraZeneca, Biogen, Celgene, Genentech (a member of the Roche Group), GSK, Merck & Co. Inc., Kenilworth, NJ, USA, Pfizer and Sanofi.
To counter concerns about the potential for both the misuse of data and for genomic-based discrimination, which may occur if data is shared with insurers or employers, many countries have enacted protective legislation. Examples include the Genetic Information Nondiscrimination Act (GINA) of 2008 in the United States (Box 6) and the Code on Genetic Testing and Insurance in the UK, which prohibits life insurance companies from forcing customers to disclose genomic information. The Finnish Biobank Act (2013) and the proposed new genome law also explicitly prohibit insurance companies from accessing the data.

**Box 6: The US Genetic Information Nondiscrimination Act (GINA) of 2008**

In the United States, the Genetic Information Nondiscrimination Act of 2008 was implemented to prevent health insurers (Title I) and employers (Title II) from discriminating against individuals on the basis of their personal genetic information. The law specifies that genetic information includes ‘family medical history, manifest disease in family members, and information regarding individuals’ and family members’ genetic tests’ and amends the Health Insurance Portability and Accountability Act of 1996 to define genetic information as health information. Title I covering health insurance is implemented by the Internal Revenue Service, Department of Labor and Department of Health and Human Services, while Title II covering Employment is implemented by the Equal Employment Opportunity Commission (EEOC).

**Health Insurance (Title I)**

Under Title I of GINA, health insurers are prohibited from using genetic information to inform any decisions on ‘eligibility, coverage, underwriting or premium-setting decisions’. Health insurers are also prevented from asking individuals or their family members to undertake a genetic test or to provide genetic information.

**Employment (Title II)**

Under Title II of GINA, employers are prohibited from using genetic information to inform employment decisions, such as whether to hire, fire or promote an employee, the tasks and responsibilities that an employee may complete and the compensation that an employee may be given. Employers may also not ask to receive genetic information or genetic tests from current or prospective employees.

Source: National Human Genome Research Institute, 2019.

**Legislation banning discrimination based on genomic data has been implemented**

At the European level, legislative responses banning discrimination based on genetic data go back to the 1990s, with the adoption of the Oviedo Convention on Human Rights and Biomedicine (Council of the European Union, 1997) and the Charter of Fundamental Rights of the European Union (European Union, 2016). The Oviedo Convention was the ‘first legally-binding international text designed to preserve human dignity, rights and freedoms, through a series of principles and prohibitions against the misuse of biological and medical advances… it bans all forms of discrimination based on the grounds of a person’s genetic make-up and allows the carrying out of predictive genetic tests only for medical purposes’ (Council of the European Union, 1997). Since its development, the Oviedo Convention has been ratified by 34 countries across Europe.

**Protection of intellectual property rights should aim to maximize public benefit while stimulating investment**

The use of genomic data also raises challenges over intellectual property rights. Policy developments in the domain of human genetics should aim to maximize public benefit while allowing a level of intellectual property protection to stimulate innovation and investment that is reasonably necessary to achieve that benefit (Borry et al., 2018) (see Box 7).
Box 7: Genomics and the protection of intellectual property rights

Patents provide protection for intellectual property of an invention for a limited period, providing a means for recouping the time and money invested in its development. With an increasing number of participants (individuals, researchers, commercial sector) involved in the production of genomic data and associated technologies, ambiguity can arise as to who has (first) right to benefit commercially, financially and academically.

The United States’ Supreme Court ruled in 2012 that genetic sequences that are the same as those found in nature cannot be patented (Lai, 2015; Guerrini et al., 2017), although one that has been modified sufficiently may be. Some related products, such as tests for certain genes, can be, as with BRCA1. There are some concerns that the dilution of patent protection in the US may cause companies to instead protect genomic discoveries as a trade secret, where ‘any information that derives independent economic value from not being generally known to or readily ascertainable by others and is the subject of efforts to maintain its secrecy’ (Guerrini et al., 2017). This may stifle the translation of genomic information into clinical care as, by its very nature, trade secrets cannot be disclosed or they will lose their legal status and, unlike patents, trade secret rights last indefinitely and not for a defined period (Guerrini et al., 2017).

There are also restrictions on patenting genetic material in Europe (Cole, 2015), but this is based on a 1998 Directive, which does not fully address the current possibilities. So far, Europe has seen relatively little patent enforcement against publicly funded health services. However, when the Unitary Patent takes effect, which is currently expected in early 2022 (European Patent Office, 2020), and patent owners can enforce their rights throughout Europe with a single legal action, the genomics industry may become more litigious. As a result, laboratories may not be able to afford to carry out freedom-to-operate patent searches every time a new lab-based test is introduced. It should be considered whether maximizing public benefit would require more strategic innovation management.

However, much of the intellectual effort in future years will likely be spent not on the isolation and characterization of individual molecules, as most information on the human genome at a single-gene level is already widely available, but will instead focus on relating biomarkers to disease risk. It may well be, therefore, that in the future, some may consider that intellectual property rights would be better protected through the use of copyright and the protection of proprietary databases rather than through the patent system.

Box 8: Potential harms and benefits of DTC-GT

Proponents of DTC-GT argue that providing genetic information directly may result in improved compliance with advice on healthy behaviour and screening. However, a 2011 study of people who underwent consumer genome-wide testing in the United States found that such testing did not result in any measurable short-term changes in diet or exercise, or use of screening tests (Bloss, Schork & Topol, 2011). Others suggest that the tests have potential to cause unnecessary harm, including anxiety and distress, inappropriate responses (e.g. change of prescription medication) and use of unnecessary and expensive screening and medical procedures. Given the costs, many observers argue that the tests may raise consumer protection issues (Bloss, Schork & Topol, 2011). However, the results of a 2017 systematic review show that there is currently little or no evidence for serious adverse psychological responses among consumers, and only a small percentage of people show potentially inappropriate responses (Stewart et al., 2018). There are additional consumer risks if the results are inaccurate or are not communicated effectively to the individual.

Interviews with clinical geneticists in the UK identified concerns about the consequences arising from patients obtaining their own genomic data through DTC testing on clinician time and public health care resources, and especially the demands for follow-up action by the health system (Finlay, 2017). It is important to consider the potential opportunity costs for the health service and the potential for entrenching inequalities whereby limited diagnostic resources are monopolized in following up findings of dubious importance among generally higher-income populations. Having said that, the authors of the UK study comment that they experienced difficulty recruiting clinical geneticists with experience of DTC-GT, suggesting that the potential burden on the health care system may not in fact have materialized so far. Of course, it should also be recognized that there may be some instances where genomic advances may be used to improve treatments for diseases that predominantly affect low-income populations. A promising example is the discovery of CRISPR/Cas9 (a genome editing tool) that may give rise to genome engineering applications to correct mutations that lead to sickle cell disease. In this context, DTC-GT may play a role in expanding access to genetic testing for populations that may benefit from its findings but be disadvantaged in accessing health care services.

Data sharing with individuals through DTC-GT

DTC-GT can facilitate access to genetic testing but there are concerns over potential harms

Health-related DTC-GT can currently be ordered either by a health care provider, or in some cases without any involvement of medical professionals. In the latter case, DTC-GT (e.g. a testing kit) is often ordered by consumers online. Subsequently, the consumer submits a biological sample (saliva or hair) to the commercial company for DNA to be extracted from it and analysed. In return, the consumer is provided with a test result, usually via a website or email.

A systematic review, conducted as part of the Innovative Partnership for Action Against Cancer – Joint Action (IPAAAC JA), reported that European citizens have an overall low level of knowledge on DTC-GT, but a high interest in its purchase, mainly to find out their risk predisposition to common diseases, such as cancer, cardiovascular diseases or diabetes (Hoxjah et al., 2020). However, the European citizens group has raised concerns about data privacy, data sharing and test result confidentiality and reliability, concerns shared by many clinicians and policy-makers (Hoxjah, Stojanovic & Boccia, 2020; see Box 8). On the one hand, DTC-GT can in theory support greater access to genetic testing and allow consumers to make healthy lifestyle decisions and control the use of their genomic data. On the other hand, the frequent absence of medical supervision and genetic counselling raises concerns around the misinterpretation of test results, which may, contrary to the original goal, lead to misinformed decision-making or demands for follow-up action by the health system (Finlay, 2017). Other concerns relate to issues such as clinical validity and the utility of DTC-GT, protection of minors, implications for donor conception as anonymity can be less guaranteed in countries where this is provided, data sharing, ownership of genomic data and implications for use outside of health care, such as in forensics. In Europe, many of these concerns have been addressed through the European Commission’s In-Vitro Diagnostic Regulation implemented in 2017 (in effect from 2022), which regulates all tests that provide information on ‘predisposition to a medical condition or a disease’ (Article 2(2)) (see Box 9).
Concerns over privacy can be countered by stronger national regulation

A particular concern regarding DTC-GT is the data management and data-sharing practices of commercial companies. There have already been instances where ‘de-identified’ genomic data collected through DTC-GT have been sold for profit to pharmaceutical companies; even if this data is ultimately used for research purposes, it may not comply with the original data usages intended by consumers (Seife, 2013). A number of these companies have recently pledged to be more transparent when they share users’ data in order to address growing privacy concerns in the United States, in particular following the use of a DNA-comparison service to track down at least one person believed to have committed serious crimes (Romm & Harwell, 2018). Some countries have also made efforts to regulate data-sharing practices of DTC-GT companies. Nevertheless, much scope remains to improve and develop regulation to ensure that data collected through commercial enterprises is used in fair, transparent and ethical ways that meet the expectations of consumers (see Box 9).

Box 9: National DTC-GT regulation in European countries

Member States have taken various approaches to regulating and restricting genetic testing

Currently, specific legal instruments for DTC-GT, both at EU and national levels, have largely not yet been implemented. The majority of EU Member States nevertheless have some national legislation related to genetic testing that could apply to DTC-GT. In some countries, such as France, Germany, Portugal and Switzerland, DTC-GT is virtually banned, with the types of tests available to consumers restricted and the involvement of health professionals mandatory in most cases (Kalokairinou, 2018; Hoehaj et al., 2020). Other countries (e.g. Luxembourg, Poland, Romania) have conversely not implemented any laws specifically targeting genetic testing of any kind; this means that any limitations on the selling and use of DTC-GT relate to other regulations surrounding health care provision, informed consent and patient rights. In some places, the regulation of genetic testing in clinical settings and DTC-GT differ. In the UK, for example, predictive testing in the NHS may only occur after genetic counselling, but there are no specific regulations targeting commercially available DTC-GT.

Most national laws apply to clinical genetic testing rather than DTC-GT

National regulation is often influenced by international documents, such as the Council of Europe’s internationally binding Convention on Human Rights and Biomedicine (also known as the Oviedo Convention, which came into force on 1 December 1999) and its Additional Protocol on Genetic Testing for Health Purposes, which came into force on 1 July 2018, for the first time dealing with DTC-GT at an international level. There are also the OECD’s guidelines on quality assurance for molecular genetic testing (OECD, 2007). Following these international documents, at a national level particular importance has been assigned to restricting the way some genetic testing is performed and on providing medical supervision to assist patients in making informed health care choices. Most national laws apply to clinical genetic testing, e.g. in health care systems, where laboratories and clinical services are subject to professional or internal supervision, oversight and controls. In many cases it is unclear whether these laws are applicable in the commercial DTC-GT context.

IVDR is a European level legal act that will affect regulation of DTC-GT

In Europe, there is currently no common legal framework specifically targeting DTC-GT. There are, however, consumer protection laws and more specific laws on In-Vitro Diagnostic (IVD) devices affecting and influencing the regulation of DTC-GT at the EU level (see Box 10).

Box 10: The In Vitro Diagnostics Regulation (IVDR)

In 2017, the EU Parliament passed the in vitro diagnostic regulation (IVDR), which aims to regulate the safety and performance of IVD devices; this includes all tests that provide information on ‘predisposition to a medical condition or a disease’ (Article 2(2)) (IVDR, 2017)), thereby covering almost all DTC-GT. The regulation is due to come into force in May 2022 and will see genetic tests moved into a higher risk category than before. Under the IVDR, genetic tests are classified as Class C devices, meaning that prior to reaching consumers, they must undergo a pre-market assessment by a notified body and must meet safety and performance requirements to demonstrate clinical validity. If devices fulfil essential requirements, they are granted a certificate of conformity (CE) and can be sold and used in the EU market. Importantly, the IVDR also applies to companies outside the EU that want to sell their products (e.g. via the Internet) to individuals residing in the block. The IVDR also regulates advertising of devices, meaning that advertising of products cannot contain misleading claims.

The purpose of the IVDR is to support the functions of the internal market and prevent unsafe and inefficient IVD devices from entering the market. Thus, the regulation includes, for example, risk-based classification rules for products, technical file requirements, accreditation and clinical evidence requirements, and updated roles and responsibilities for different actors. It is notable that Article 4 of the IVDR covers specific requirements on genetic information, counselling and informed consent for human genetic tests, but is not detailed as regards clinical arrangements. Instead, EU Member States are able to apply national rules on informed consent and genetic counselling in recognition of the principle of subsidiarity and Member States’ rights to regulate clinical practice.

The iPAAC have called for a strategy to be developed on how to deal with DTC-GT within the health system

The Innovative Partnership for Action Against Cancer (iPAAC), which is a funded initiative under the Third Health Programme 2014–2020, also covers DTC-GT, in particular considering the literacy and legal position of citizens and health care professionals (iPAAC Joint Action, 2018). The main aim of the iPAAC project is the implementation of innovative approaches to advance cancer control, with a key focus on implementation processes among EU-level policymakers at local, regional and national levels.
4. The way forward? Discussion and conclusions

Human genomic information is highly sensitive and there are some concerns that uncontrolled access to it may lead to privacy violations, discriminatory practices and other detrimental effects. However, without access to it, people may lack information which could translate into immense health benefits. Already today, genomic information is used to inform neonatal screening, preconceptional screening and prenatal screening, as well as in a number of important applications in health care that enable better diagnosis, treatment and risk stratification. Yet, much of the potential of genomics remains unknown. As the amount of collected genomic information grows, new applications are being uncovered by scientists and increasingly applied into clinical practice.

It is important that health systems create an enabling environment for these scientific advances to continue, while protecting patients and consumers from their genomic information being used in harmful ways. This requires appropriate regulation and education, which may be complex and challenging but, as shown, not impossible. It also requires maintaining an active dialogue with all stakeholders to build a broad societal trust in genomics.

Building and maintaining trust with patients and the public

As outlined in this brief, many of the issues raised by genomics are not new, but their scale and scope, as well as the perceived power of genomic information, mean that specific action is needed to maintain public trust and patients’ expectations in relation to how genomic information is provided, processed and used. After all, a trustful society where everybody, both public and private actors, sees the added value of genomics and the necessity to collaborate is needed to achieve its full potential. Public and patient trust will, however, only be earned if the benefits and potential risks of genomic research are well understood and people have confidence that their data will not be misused (Presidential Commission for the Study of Bioethical Issues, 2012). This not only requires strong legislation and regulations to address these issues, but also active engagement and continuing dialogue between various stakeholders over time, including with individual patients and other contributors of genomic information, as well as with society more widely. This should be based on the existing values and principles of European health systems, but will require careful rethinking to adapt to the particular challenges and potential power of genomics, as well as the specific context of different health systems and the people and processes involved in genomic research and processing in each country.

It should also be noted that currently there is too often a gap between the levels of genomic knowledge and literacy of the public and the information they may receive. Providing genomic education to patients will become ever more important as genomics plays an increasing role in clinical care. Just as patients should have at least some understanding of the health care procedures they are receiving, they should also have a basic understanding of genetic testing to reduce misunderstanding of results and so they are aware of how they may benefit from genomic advances. As genomics penetrates further into routine health care, patients, the public and other stakeholders will require the necessary knowledge and information to become fully informed and active participants in these processes.

Improving clinician knowledge, education and training on genomic medicine

As the use of genomics in health care becomes ever more prevalent, the number of health professionals that will be called upon to interpret and order genetic tests and provide advice on genetic matters will continue to grow. Health systems will need to respond by not only developing the health workforce to include greater numbers of genetic medicine specialists, genetic counsellors, clinical bioinformaticians, researchers and analysts, but also by improving the genomic literacy of non-specialist physicians, nurses and other clinicians through specialist cross-disciplinary education and training.

So far, professional training for specialists in medical genetics has not yet been standardized across the EU, even though specialist medical training in medical genetics was recognized at the EU level in 2011 (European Commission, 2018a). However, the European Board of Medical Genetics has developed standards and curricula for training of specialists in medical genetics (in collaboration with UEMS Section of Medical Genetics), laboratory geneticists and genetic counsellors and nurses.

For non-specialist clinicians, genomics education in many countries has not kept pace with rapid advances in genomic research, meaning many of the potential uses of genomics in health care cannot yet be fully captured. The available literature suggests that many physicians may have limited understanding of genomics, including those who may be users’ first port of call for help with interpretation of genetic test information (Finlay, 2017). This is problematic because the meaning and implications of the data are often complex and interpretation often requires comprehensive understanding of the topic. Moreover, health professionals with limited education and training will face significant challenges in conveying complex genetic information to patients.

Much scope therefore remains across Europe to integrate appropriate training on genomics in health care into the core medical and nursing curriculum to increase provision of specialist training (Authority of the House of Lords, 2009). This training should begin with a needs assessment and address both the fundamentals of genomics, legal, ethical and practical concerns regarding privacy concerns and data sharing, and specific competencies that will be required in their field of practice. Given the rapidly changing genomics landscape, education and training should be flexible and dynamic to keep pace with future developments in the field.
An example of current good practice in this area includes the Genomics Education Programme established in England that is available for all health professionals (Health Education England, 2019a, 2019b).

Adapting the health system information infrastructure to realize the potential of genomics

What is also needed to realize the potential of genomics is linking genomic data to other forms of information at the individual and population levels. This in turn depends on the wider information infrastructure of health systems. European health systems have made progress in recent years towards more effective use and analysis of data, alongside wider use of information and communication technologies for health (‘e-health’) and AI, but much work still remains to be done (European Commission, 2018a). Realizing the potential of genomics is therefore linked to the wider digitalization strategies and progress of health systems.

Progress so far with digitalization of health systems has been slow, although in some countries it has been recently accelerated under the COVID-19 pandemic. The use of digital technologies raises issues at many levels. This not only concerns technologies and their interoperability but also the wider issues of complex systems change and public trust in the technologies and how they are being used. The slow adoption of digital technologies when the rest of society is digitalizing rapidly may well be a cause of public dissatisfaction and mistrust, if people feel health care is lagging behind, paternalistic and unprofessional. Genomic information can be seen as an extension of this process, and it is vital to learn policy lessons from the experience of digital health so far, including the importance of broad engagement in processes and understanding the complexities of the new technologies.

A health innovation system adapted for genomics

Another issue on which policy-makers need to focus their attention in order to maximize the potential of genomics is rethinking the wider health innovation model itself. Genomics and other digital technologies, robotics and AI represent challenges to our existing system of generating innovations in health. The existing model (in particular for medicines development) is based on a lengthy and expensive process of research and development; the high costs that this involves can nevertheless represent good value in that they can be spread over as many patients as possible.

However, the added value of genomics and personalized medicine might sometimes be the opposite: value through generating diagnostics and targeted treatments, which may result in these being applicable for a small number of people only. This logically means that either the initial costs of research and development must become much smaller than they currently are (of which there appears to be no immediate sign), or the costs of personalized medicine per person will in such cases inevitably be very high. How can this be addressed?

One possibility is that personalized medicine can help by making the use of treatments more efficient through more accurately targeting those patients who will benefit. But if this only means targeting new treatments, it merely exacerbates the problem, by narrowing costs onto an even smaller pool of people. Greater efficiency through genomic information therefore would have to involve better targeting of existing treatments in order to have the potential to improve population health and reduce costs for health systems. Another possibility is that genomic information enables earlier diagnosis and pre-symptomatic preventive intervention or treatment (e.g. as is already the case for cancer screening and familial hypercholesterolemia (Luirink et al., 2019)), and that this earlier intervention might save costs later. For example, the diagnosis and treatment of rare diseases is often lengthy and expensive; the use of genomics might enable the time to be shortened and costs to be saved. Genomics might also improve the effectiveness of existing treatments (e.g. the use of pharmacogenomics might reduce side effects, particularly the serious and even fatal ones) and reduce the use of ineffective treatments, which will also lead to cost savings.

Another approach is to reconsider the fair allocation of public and private goods throughout the health innovation process. Currently, people who contribute to clinical research by providing their genomic information do not typically2 receive any benefit from the subsequent research and development uses that are made of that information. Information is provided as a public good, even when it is used in research and development that leads to profit or private benefit. This is a wider issue that has been raised in relation to public funding of basic research from which private benefit is drawn without the public receiving a return on their initial investment (Mazzucato, 2016). Taking a broader view, one could argue that public benefit is returned through taxation – although, of course, private profit does not necessarily or even very often generate tax revenue in the places that financed the research. However, there is no such return to individuals contributing their genomic data for wider purposes of research. Fair allocation might not involve linking benefits back to individual contributors, but for the potential of genomic innovation to be realized, a wider discussion about the appropriate balancing of public and private goods throughout the health innovation system will become vital.

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2 In some cases, participation in clinical research brings benefits, including receiving innovative treatment and follow-up.
In reality, the terms personalized and precision medicine are often used interchangeably. Personalized gives the term an added dimension in that it places the individual concerned at the centre of decision-making about health and disease.

Definitions of key concepts

Genetics is the branch of science concerned with the study of inheritance, the genes underlying it and their functions. Genomics refers to the study of the entire genome and the large amounts of corresponding data generated from it (see Box A1 on the difference between genetics and genomics). Genomics has the potential to offer a greater understanding of the implications of our genetic make-up for our health, particularly for diseases and conditions with multifactorial causes.

Box A1: Genetics vs genomics – what is the difference?

Genetics is the science of inheritance, the genes underlying it and their functions. Genetics as a science has existed for the last century, long before the structure of DNA was understood and before molecular access to the genome was available. Genetics involved the study of single genes and their variations as a cause of inherited single-gene (Mendelian) disorders, such as Fragile X syndrome, cystic fibrosis and Huntington’s disease. While each of these disorders alone is relatively rare in the population based on the EU definition of rare diseases. It has been estimated that, taken together, approximately 6–8% of the European population will be affected by a rare disorder at some point in their life (European Commission, 2008).

Most common chronic NCDs are multifactorial, caused by numerous variants in the genome that interact with each other and with a range of environmental factors. Moreover, there is a significant genetic component for predisposition to many, if not most, infectious diseases as well. To gain more knowledge about these diseases, researchers work with genomic methods. Genomics involves genome-wide studies, in other words analysing the entire genome and how these genes interact with each other and with environmental factors. Hence, genomic methods allow researchers to explore the causes of common diseases with complex etiology, such as cancer, diabetes or heart disease, which have multifactorial determinants including genes, lifestyle behaviours and other environmental influences.

Source: Authors, drawing on Molster et al., 2018.

With the explosion of -omics and big data technologies over the past decade, huge amounts of individual and population information, including, but not limited to, genomics, have the potential to be harnessed to deliver the ‘right treatment to the right patient at the right time’. Treatments can be tailored to individuals (which is termed personalized or precision medicine) or specific groups of patients, where people are divided into subgroups according to various stratifiers, including genetic variants (giving rise to the term ‘stratified medicine’). Furthermore, these new technologies and the data they generate and use have given rise to a race to determine how they can be used to improve health outcomes at the population level. This emerging public health field has been termed ‘precision public health’ (Molster et al., 2018; Bilkey et al., 2019b).

However, although many genomic tools and technologies have been developed, there has often been limited evidence on their validity and utility. It is therefore essential to evaluate existing and emerging knowledge, tools and technologies in order to determine which are actually beneficial to individual and population health, and how they could be appropriately implemented in health systems. This requires an objective evaluation of the potential benefits against the potential harms, and the resources required for implementing them (Molster et al., 2018). Recognition of this need has given rise to the concept of public health genomics, defined as: ‘the responsible and effective translation of genome-based knowledge and technologies into public policy and health services for the benefit of population health’ (Burke et al., 2006).

Selected key applications of genomics

Genomic medicine is an emerging field and translating the new information and knowledge it brings into patient care will likely take many years. Nevertheless, findings are gradually starting to be used to inform prevention and treatment strategies in some fields, most notably in the diagnosis of rare diseases and understanding and developing targeted therapeutics in cancer care (Table A1).

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1 EU regulation on orphan medicinal products (1999) defines rare diseases as conditions with a prevalence of not more than 50 per 100,000 population (European Union, 2000).

2 A field of study in biology that ends with -omics, such as genomics, transcriptomics, proteomics, etc., which aims to detect, characterize and understand complete biologic molecules, often to give insights into disease pathways or processes.

3 In our view, personalized medicine has now evolved to have the same multifactorial components as precision medicine, but the use of the word personalized gives the term an added dimension in that it places the individual concerned at the centre of decision-making about health and disease. In reality, the terms personalized and precision medicine are often used interchangeably.
Regulating the unknown: a guide to regulating genomics for health policy-makers

Genetic and molecular characteristics may be used as a basis for diagnosis and disease classification that go beyond traditional diagnostic approaches, in which diseases are defined by phenotype (i.e. presence of signs or symptoms) or physiology/pathology (i.e. presence of biochemical or histological abnormalities). Identifying specific genetic changes may facilitate diagnosis, particularly in difficult cases where there is no obvious single pathology, for example, in children with a learning disability or developmental delay. Improved diagnosis and detailed disease classification may then enable more effective and specific treatments. In some cases, it may be possible to identify small numbers of people with a high risk of a specific disease due to a rare genetic condition, in whom the onset of disease can be prevented or, if it occurs, treated early.

The development of new genetic tests may also create new opportunities for screening to detect conditions that pose a future risk to those affected. Genomics provides information which may indicate an individual’s risk of or potential resistance to future disease, thereby offering potential to stratify populations according to their genetic disease risk and to go beyond those measures normally used to stratify

| Table A1: Selected current and emerging applications of human genomic information |
|--------------------------------|--------------------------------|
| **EXISTING APPLICATIONS** | **EMERGING APPLICATIONS** |
| Diagnosis and disease classification | Diagnosis of some atypical forms of common diseases or identifying conditions that cannot otherwise be diagnosed. |
| - Diagnosis of inherited disorders based on single-gene mutations, such as cystic fibrosis; diagnosis of diseases that are difficult to diagnose; diagnosis of diseases with heterogeneous genetic background, such as developmental delay, or diagnosis of seriously ill newborns; panel testing for inherited disorders where 10–100 genes may be involved (e.g. some conditions affecting eyesight). | - Rethinking existing classification and diagnostic criteria for diseases in the light of better genomic understanding. |
| - More accurate classification of cancers into various subgroups, for example, haematological cancers or breast cancer. | |
| Guiding treatment | |
| - Specific genetic variation in cancer patients is used to determine the choice of therapy, for example, in patients with colon cancer, and to identify women who are at high risk of relapse for breast cancer. | - Using genome-wide analysis, including in combination with information obtained from patient-derived explant culture, other medical information, and using methods such as machine learning to identify clinical pharmacogenomic variation to better understand drug responses. |
| - Single pharmacogenetic variations are studied in association with initiating new medication, such as screening the CYP2D6 gene in paediatric patients given codeine, since slow metabolizers have poor analgesia and ultra-rapid metabolizers are at risk of respiratory arrest. | - Using circulating tumour DNA (ctDNA) (as a noninvasive ‘liquid biopsy’) for early detection of cancer relapse. |
| - Monitoring disease recurrence after treatment in some conditions; for example, highly sensitive tests for monitoring minimal residual disease have become standard practice in many types of leukaemia. | |
| Stratification of populations according to disease risk or resistance | |
| - Identifying high-risk hereditary predisposition in certain populations. Examples include newborn screening for rare inherited genetic conditions before clinical presentation (e.g. phenylketonuria (PKU)) and genetic testing to identify some common cancers caused by single-gene mutations (around 5% of breast cancers and 15% of ovarian cancers are caused by mutations in BRCA1 or BRCA2 genes, and around 3% of colorectal cancers arise in patients with Lynch syndrome, an inherited genetic condition). | - Risk profiling for common diseases using polygenic risk scoring (PRS) as complementary risk information for conditions such as cardiovascular diseases to help identify high-risk individuals who are not identified by traditional indicators. |
| | - Identification of composite inherited cancer risk from common and rare genetic variation patterns and modifying personal screening recommendations. |
| Sources: Authors, drawing on: van der Velden et al. (2003); Cowin et al. (2010); McDermott, Downing & Stratton (2011); Arber et al. (2016); Boccia et al. (2014). |
Policy brief

Polygenic risk scores aim to quantify the cumulative effects of several genes to measure inherited predisposition to a disease, such as cancer and cardiovascular diseases (Box A2). There is an expectation that PRS may lead to better targeting of treatment and preventive interventions.

The theoretical advantage of stratifying populations according to their genetic disease risk is that prevention programmes can be targeted or tailored to those at higher risk and therefore those who are more likely to benefit from these programmes. This, of course, raises many questions about how this might be done, given that the most effective ways to promote health and prevent disease are implemented at the population level, such as measures to address price, availability, and marketing of harmful products.

### Box A2: Cancer and personalized medicine

Cancers are defined as a collection of diseases in which abnormal cells can divide and spread to nearby tissue (National Cancer Institute, NCI). There are more than 100 types of cancer. Cancers are especially challenging to treat as every single tumour is unique and dynamic, which means they have a great potential to acquire further changes (somatic mutations) to gain resistance to given treatment.

Cancers thus require a targeted therapy, i.e. treatment that targets the cancer’s specific genes, proteins or the tissue environment, to block the growth and spread of cancer cells while at the same time limiting damage to healthy cells.

The limited success in curing malignant disease arises, in part, from insufficient understanding of the function and interplay of the genomes of the affected cells. For this reason, applications of genomics in cancer care involving the identification of somatic mutations (which can be acquired through life), that can be exploited to target therapies, have been viewed as particularly promising.

There are already several examples of success (for example, with BCR-ABL1 positive acute lymphoblastic leukemia) but also many challenges. Effective targeted treatment of solid tumours (either with experimental drugs or those approved for different indications) has been elusive and there are inevitable uncertainties about which targeted therapy to use when patients have multiple genomic variants in their cancer cells. However, next-generation sequencing (NGS) technologies have provided some clues to therapeutic targets and genomic markers for novel clinical applications when standard therapy has failed (Malone et al., 2020).

The growing volume of genomic knowledge has given rise to some technologies that are being translated into clinical practice, such as noninvasive prenatal testing (NIPT) for genetic abnormalities, some neonatal screening activities for genetic conditions, and to help individual patients, often with rare conditions. However, overall there has been relatively little impact on public health practice (Molster et al., 2018). This is mainly because, while genomic studies on common diseases and traits have identified many associated gene variants (so-called polygenes), most, on their own, have a very small influence on a phenotypic trait. This is due to most common diseases being the result of complex interactions between multiple genes and environmental factors. Furthermore, the genetic variants that contribute to a given disease, and how they are expressed, vary within and among populations, as might the relative significance of genetic and non-genetic factors.

Nevertheless, individuals who carry multiple specific genetic variations, i.e. have a high PRS, may have a very high risk of disease. These individuals might benefit from specific prevention and surveillance measures, although this will depend on many other considerations, such as whether there is an effective means of prevention or treatment.

Progress in FinnGen and other large-scale population genetic studies (Mars et al., 2020) has recently demonstrated that the integration of genome-wide genetic variation patterns can help identify a much larger group of individuals meeting ‘high-risk’ criteria for whom screening and other interventions have public health utility – although, as yet, these results have not been converted into changes in medical practice.

While the polygenes identified in genome-wide association studies (GWAS) usually explain only a part of the genetic and total variability for the particular trait, PRS may hold some possible promise as a means of stratifying the population into high and low risks in certain circumstances, which may justify various interventional and preventive measures⁶. This is already done in some countries for women identified as having BRCA1, BRCA2 and other genes associated with a higher risk of developing breast cancer. PRS may also be better at predicting the risk of certain diseases than conventional clinical risk factors (Tikkanen et al., 2013; Läll et al., 2017; Inouye et al., 2018; Schumacher et al., 2018; Mavaddat et al., 2019). They may also offer scope to be used as biological (risk) markers for certain traits that currently lack such markers. The current clinical utility of cardiovascular PRS remains undetermined, however, with the accuracy of models predicting cardiovascular disease risk found to be improved by adding PRS in some studies but not others (Khan, Cooper & Greenland, 2020) – and definitive studies integrating both conventional risk factors and genetic risk factors appropriately are uncommon (Mars et al., 2020).

While recent studies on polygenes as measures of risk for some diseases are encouraging, it will be essential that the use of these techniques in the diagnosis and treatment of individuals be subjected to the same evidence-based scrutiny as any other investigations. This may be challenging given the complexity of conducting evaluations in this area (Molster et al., 2018). The importance of accumulated evidence in adopting such personalized prevention approaches before implementation in health care has been emphasized by the recommendations of the Personalized pREvention of Chronic Diseases (PREcED) Consortium (Boccia et al., 2019). A set of recommendations for policy-makers, scientists and industry has been provided (see Table A2).

⁶ Since most GWAS and PRS are undertaken in white European populations, their applicability to other populations is often limited (Martin et al., 2019).
Regulating the unknown: a guide to regulating genomics for health policy-makers

Direct-to-consumer genetic testing

In the last decade, citizens have increasingly been able to access some of their genomic information through commercially available DTC-GT products and services, driven by the rapid advance of genotyping\(^7\) technologies and their decreasing costs. DTC-GT can be either health-related or non-health-related. The former includes diagnostic tests for monogenic diseases, susceptibility tests for common complex disorders, carrier tests for X-linked and autosomal recessive disorders, and pharmacogenomic as well as nutrigenomic tests. Non-health-related tests include ancestry tests, athletic performance tests, matchmaking tests and other tests mostly targeted to entertain the consumer.

\(^7\) Genotyping refers to sampling specific known positions in the genome of interest, while sequencing refers to taking the whole of the variation along the DNA molecule.

<table>
<thead>
<tr>
<th>DOMAIN</th>
<th>RECOMMENDATION</th>
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<tbody>
<tr>
<td>Diagnosis and disease classification</td>
<td>R1. Personalized interventions for the prevention of chronic diseases require robust evidence of efficacy and/or effectiveness of the new technology when implemented in health care.</td>
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<td>2. Economic evaluation of predictive genomic applications</td>
<td>R2. A comprehensive evaluation of the value (outcomes/cost) of genetic and genomic applications should include evidence on the efficacy and/or effectiveness of the new technology (i.e. analytic validity, clinical validity, clinical utility), social aspects (ethical, legal and social implications, and personal utility), and context-related dimensions (e.g. economic evaluation, delivery models, organizational aspects and consumer viewpoint) to better support the decision-making process.</td>
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<td>3. Ethico-legal and policy issues surrounding personalized medicine</td>
<td>R3. The era of genomics requires that we clarify and validate the obligations and responsibilities of the research community, research participants and the general public. This can be achieved through collaboration and dissemination of high-quality ethical, policy and legal analysis. Legal interoperability is necessary to ensure complementarity of goals between researchers in different jurisdictions.</td>
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<td>4. Sociotechnical analysis of the pros and cons of informing healthy individuals on their genome</td>
<td>R3. A dedicated effort is necessary to stimulate further ethically responsible implementation of evidence-based interventions in health care, such as testing of family members in cases of hereditary cancers or cardiovascular diseases. Where guidelines for such genetic testing exist, collaboration between genetic and non-genetic health care professionals needs to be facilitated to improve implementation; education opportunities must be provided; and roles and responsibilities towards informing family members must be reconsidered so that we can achieve a truly multidisciplinary approach that can realize the potential of personalized medicine.</td>
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<td>5. Identification of organizational models for the provision of predictive genetic testing</td>
<td>R5. The integration of genetics into other medical specialties should be promoted through new delivery models involving different health care professionals (medical specialists, nurses, technicians, etc.) and new professional roles (i.e. genetic counsellors, genetic associates, genetic nurses), in order to guarantee the use and sustainability of existing and new genomic applications in practice. Roles and responsibilities (e.g. risk assessment, genetic counselling, genetic testing) should be redistributed among different health professionals to enhance work performance and the standard of care. Professional education/training in genomics medicine, laboratory quality standards and public awareness are essential factors for the successful implementation of genomic applications in practice.</td>
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Annex B: Key genomic initiatives to date

The application of genomics for research or clinical purposes relies on high-quality data being collected and stored in an organized (standardized) way. The scale of systematic gathering of genome data has increased in a number of countries in recent years (Figure A1), with those managing many genomic databases engaged in collaborative international research projects (Stark et al., 2019).

Although many of the national genomic medicine initiatives are still in their infancy, early results are beginning to be seen from some of the more well-established programmes, such as the UK’s 100,000 Genomes Project (see Table A3). National genomic medicine initiatives have taken a variety of approaches (Dankar, Ptitsyn & Dankar, 2018), with some programmes focusing mainly on rare diseases and cancer, while others pursue population-based projects and others infrastructure, such as common standards and data-sharing policies and platforms (Nicolaus, 2019). For example, Finland’s genome strategy encompasses clinical, research and commercial aims (see Box A3; an overview of national genome strategies in several other countries is provided in Table A3). In several countries, national strategies and plans for personalized, precision, or genomic medicine have been implemented (Instituto Roche, 2017) (see Box A4 for Italy’s strategy on genomics).

**Figure A1: National medical genome projects and cohorts in 2019**

Medical genomes
- Countries with active national medical genome projects
- Countries with some activity of medical genomics
- Countries planning medical genome projects

Cohorts
- National cohorts > 100k genotyped or sequenced at least 25k
- National cohorts > 100k people active collection now
- Planning national cohorts > 100k

Source: Reproduced from Birney, 2019.
### Table A3: Selected national personalized and genomic medicine initiatives and strategies

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<tr>
<td><strong>Precision Medicine Initiative</strong></td>
<td>The Chinese government confirmed plans to make precision medicine part of its Five-Year Plan for 2016–2020 as it works to prioritize genomics to drive better health care outcomes.</td>
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<td><strong>China</strong></td>
<td>Chinese Government; expected funding of CNY60 billion (EUR7.9 billion) by 2030</td>
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<td><strong>Danish Government and Regions National Strategy for Personalized Medicine 2017–2020</strong></td>
<td>Strategic action areas: (1) Transparent governance structure with nationwide involvement. (2) Clear legal framework addressing ethical principles and data privacy and security. (3) Patients and citizens must be involved. (4) A technological infrastructure with secure, efficient and equal access. (5) Genomics research must be international and deeply integrated in the health care system. (6) Tools and competencies to use genetic data. (7) Attractive development in relation to personalized medicine.</td>
<td>Established the National Genome Centre within the Danish health care system. Builds on previous investments in biobanking, sequencing and data infrastructure, and research.</td>
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<td><strong>Denmark</strong></td>
<td>Danish Ministry of Health and Regions; initial funding of DKK100 million</td>
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<td><strong>Estonian Genome Project</strong></td>
<td>The project was proposed as being of huge cultural value and leading in this area in global research. It has collected over 50,000 samples (5% of the adult population) and links this to clinical and survey data to form a rich data set. Genotyping analysis has been performed on these samples, along with sequencing in a proportion, and with additional samples and investigations in many. There are ambitions to grow it further to cover a significant percentage of the population and embed genomics within the health system as part of clinical decision support. It has gathered significant awareness and support across a large proportion of the population.</td>
<td>Continues and develops the work over the past 15 years in biobanking and eHealth. Established through legislation in the Human Genes Research Act. Operates through a government-owned company, EGeen.</td>
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<td><strong>Estonia</strong></td>
<td>Estonian Government</td>
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<tr>
<td><strong>NHS England Personalised Medicine Strategy</strong></td>
<td>Aims aligned to Five Year Forward View and health sustainability: (1) Improved prevention based on underlying predisposition. (2) Earlier diagnosis of disease as a result of identifying abnormality earlier. (3) More precise diagnosis based on cause. (4) Targeted interventions through the use of companion diagnostics to identify and stratify effective treatments.</td>
<td>Builds on the strategy of the 100,000 Genomes Project, in which NHS England is a partner.</td>
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<tr>
<td><strong>England</strong></td>
<td>NHS England leads the National Health Service in England</td>
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<th>DOMAIN</th>
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| Finland’s Genome Strategy | The aim of the strategy is to:  
(1) Make Finnish health care more effective through better and more targeted care, with integration of genomics in clinical care, individuals able to make use of their genomic data, and a containment of health care costs and better allocation of resources.  
(2) Researchers will have entirely new opportunities for utilizing genomic data.  
(3) Transform Finland into an internationally attractive environment for research and business in the field of genomics. | Establishing a National Genome Centre to implement the Genome Strategy, including the development of a national genome reference database.  
As part of the Health Sector Growth Strategy, the Ministry of Social Affairs and Health is charged with establishing national centres/clusters of excellence (such as cancer centre, neurocentre, drug discovery centre). |
| France Médecine Génomique 2025 | Targets of the 2025 France Genomic Medicine Plan:  
(1) To position France among the leading big countries in the field of genomic medicine within the next 10 years, with the aims of exporting expertise and developing a strong medical and industrial framework.  
(2) To establish a generic care pathway with access to genomic medicine for all French people affected by cancer, a rare disease or a common disease.  
(3) To be capable by 2020 of sequencing 235,000 genomes a year for rare diseases and cancer, with growth beyond 2020 to cover common diseases. | Led by the National Alliance for Life Science and Health (Aviesan) consortium.  
Development of a hub-and-spoke model, with regional sequencing centres and a central reference centre for innovation, assessment and transfer (CRefIX). |
| Personalised Medicine – Action Plan | Strategic funding for research into personalized medicine. Targeted across R&D, from biomarker validation through to therapies and service implementation. Main goal is for patients to benefit more quickly. Ethical, legal and economic challenges and engagement and information platforms are also included within this. | Predominantly operates through an open competitive research funding programme. |
| National Plan for Innovation of the Health System based on -omics sciences | The Plan aims to support the Italian NHS in order:  
(1) To increase awareness of all stakeholders on the innovation of -omics sciences and the effects on the health of individuals and populations, enhancing the capacity of society to cope with the cultural, ethical, psychological aspect of the ‘genomic revolution’.  
(2) To put in place a strategy of ‘government of innovation’ of genomics and related fields.  
(3) To evaluate and implement the opportunities currently offered by genomics and the other -omics sciences for the health of the population. | The National Centre for Disease Prevention and Control (CCM) supports the Italian Ministry of Health, for the implementation of the National Plan. The CCM is attached to the General Directorate for health prevention of the Italian Ministry of Health. |
### 100,000 Genomes Project

**UK (established in England in 2012, with Northern Ireland joining the partnership in 2015, Scotland in 2016 and Wales in 2018)**

Funded primarily by the National Institute for Health Research and NHS England. Additional funding from The Wellcome Trust, Cancer Research UK and the Medical Research Council; funding in excess of GBP300 million to date.

Sequencing and analysis of 100,000 genomes to inform the diagnosis of patients with cancer and rare diseases. Its four main aims are to:

1. Create an ethical and transparent programme based on consent.
2. Bring benefit to patients and set up a genomic medicine service for the NHS.
3. Enable new scientific discovery and medical insights.
4. Kick-start the development of a UK genomics industry.

One of the most ambitious and advanced national projects, encompassing clinical implementation, research and commercial aims. It builds on previous initiatives, such as the UK Biobank, and operates through a government-owned company, Genomics England.

### Precision Medicine Initiative (All of Us)

**USA**

Government; initial funding of over USD200 million.

The aim is to enrol 1 million or more volunteers to enable research for a wide range of diseases and increase understanding of healthy states. Scientific opportunities presented by All of Us include the ability to:

1. Develop ways to measure disease risk based on environmental and genetic factors.
2. Pharmacogenomics.
3. Biomarker identification and validation.
4. Use mHealth technologies to correlate activity, physiological measures and environmental exposures with health outcomes.
5. Develop new disease classifications and relationships.
6. Empower study participants with information to improve their health.
7. Create a platform to enable trials of targeted therapies.

Operated from within the structures of the National Institutes of Health (NIH). Committed to engaging multiple sectors and forging strong partnerships with researchers, patient groups and the private sector. Setting the foundation for new ways of engaging research participants, sharing health data and information, and employing technology advances to mine the information for comprehensive results.

Box A3: Finland’s strategy on genomics
The Finnish Genome Strategy, published in 2015, set out a vision that: ‘In 2020, genomic information will be effectively used in Finland to achieve population health benefits.’ This vision aligns with the Health Sector Growth Strategy for Research and Innovation Activities and the national e-Health and e-Social Strategy. It emphasizes data utilization, whereby Finland should use genomic data to generate high added value for its citizens.

The genome strategy has seven main goals (Figure A2), four of which are enabling and three of which are ultimate goals. The enabling goals relate to ethical principles and legislation, the integration of genomic research into health care, the ability of health care professionals to apply genomic data, and the development of information systems that will enable efficient utilization of the data. Their achievement is expected to create the necessary conditions for maximum use of genomic data in health care, research and commercial activity, as well as by individuals.

Ongoing work includes drafting the Genome Act, which will be the legal basis for establishing a national genome centre and a centralized genomic database. The aims of the Act, which is intended to come into force in 2022, are the following:

- Support the responsible, equal and secure use of genomic data for the benefit of wellbeing and health.
- Establish the Genome Centre – a centre of excellence.
- Establish a national centralized genomic database, where genomic data produced by health care and biobank research will be stored.
- Support the use of genomic data for health care and research purposes.
- Regulate genetic testing.

Box A4: Italy’s strategy on genomics
Two policy documents published by the Department of Prevention of the Ministry of Health defined governance planning for personalized medicine in Italy.

The first National Plan for Public Health Genomics was published in 2013, with the support of the Italian Network for Public Health Genetics (GENISAP Network). The aim of this plan was to provide general guidelines to facilitate the governance of genomics in public health in the NHS. The Italian guidelines were based on three strategic pillars:

1. Systematic health technology assessment (HTA) of genetic tests for complex diseases in use and a pre-marketing assessment of those not yet currently available.
2. Promotion of genomics education for physicians (GPs first) and capacity building for all potential stakeholders in health care provision and management.
3. Promotion of basic genomic health literacy in the general population, in order to raise awareness of potential benefits, limits and risks of genomic technologies.

The second milestone in the public health genomics policy was the publication, in 2017, of the Italian Plan for Innovation of the Health System based on -omics sciences. This Plan outlines the ways in which innovation in the -omics field might reshape the Italian NHS in the areas of prevention, diagnosis and care, taking into account effectiveness (evidence base) and sustainability (cost-effectiveness) of the NHS to improve the health of the individual and the population.

Figure A2: Goals of Finland’s genome strategy

The Italian Plan aims to support the NHS in order to:

- Increase awareness of all stakeholders about the innovations in the -omics sciences and their effects on the health of individuals and populations, enhancing the capacity of society to cope with the cultural, ethical and psychological aspects of the ‘genomic revolution’.
- Put in place a strategy of ‘government of innovation’ in genomics and related fields.
- Evaluate and implement the opportunities currently offered by genomics and other -omics sciences for the health of the population.

Source: Simone et al., 2013; Boccia et al., 2017.

At the European level, there have been a number of collaborative initiatives to advance genomics research. Among the most ambitious is the ‘1+ Million Genomes’ initiative, which saw 13 European countries sign a declaration of cooperation in 2018, aimed at establishing a mechanism to provide access to at least 1 million genomes by 2022 (Saunders et al., 2019) for improving disease prevention, allowing more personalized treatments and providing a sufficient scale for new clinically impactful research (see Box A5). The number of signatory countries has risen to 23 by the end of 2020.
The Beyond 1 Million Genomes (B1MG) project was established as a support and coordinating structure for the 1+ Million Genomes initiative. Collectively, the initiative’s signatory countries have committed to establish a cross-border federated network of national genome collections associated with phenotypic data with the purpose of advancing health and medicine practices across Europe (for more information see https://b1mg-project.eu).

**Box A5: The ‘1+ Million Genomes’ initiative**

In April 2018, 13 European countries signed a declaration of cooperation ‘Toward access to at least 1 million sequenced genomes in the EU by 2022’ (also known as the ‘1+ Million Genomes’ initiative). Through this declaration they agreed to, by 2022, have at least 1 million sequenced genomes, to map research and clinical genomic databases that exist within their national borders as well as supranationally, and make the genomic data stored in those databases accessible in the EU, thereby providing proper scale for research with clinical impact (European Commission, 2018b). The initiative builds on existing national and European initiatives to ensure that citizens, researchers and health systems in Europe can benefit from the full potential of genomics to advance targeted health care interventions, leading to better prevention, early diagnosis and treatment of diseases. The initiative has two core purposes: supporting research as well as enabling genomics-led cross-border health care. It is too early to judge the impact of this collaboration, although some of the anticipated benefits include:

- bringing together decision-makers, fragmented infrastructure and expertise
- maximizing the investments already made at national level (particularly in sequencing, biobanking, data infrastructure and data governance structures and regulation)
- reaching a larger scale for research in order to facilitate new clinically impactful research
- improving cancer treatments, improving prognosis for rare diseases and preventing common and complex diseases
- improving the use of pharmacogenomics ensuring that health systems in Europe can benefit from existing initiatives and databases as well as infectious diseases (including COVID-19)
- maintaining the EU at the forefront of genomic medicine

Source: European Commission, 2018b.

International collaboration in ways of integrating genomics into clinical practice is, in general, still in the early stages of development, and government actions have so far been largely uncoordinated and inconsistent (Horgan, Romao & Hastings, 2017). This has led to calls at the EU level to foster cooperative development and harmonization of policy on translating genomics into health care among the Member States. The World Economic Forum has, however, developed a Precision Medicine Programme, which aims to support the development of policy frameworks and governance protocols to realize the benefits of precision medicine for society, while reducing risks. Many initiatives began as research projects, but some also focused on clinical care or generation of data for commercial uses, most commonly for drug discovery (Horgan, Romao & Hastings, 2017).
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