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Public Health Genomics as a Societal and Political Challenge

Dirk Stemerding & André Krom (eds.)

The aim of this Expert Paper is to contribute to the policy deliberations of the *Future Panel on Public Health Genomics* which has been established as part of the European PACITA project. The Future Panel consists of parliamentarians from different European member states (see Appendix 1). As a starting point for the work which led to this Expert Paper the Future Panel formulated a list of questions and issues they considered particularly relevant for setting a policy agenda for public health genomics. To indicate how the contents of this paper relate to the questions and issues raised by the Future Panel, we have highlighted these questions and issues in the relevant sections of the paper by including them in text boxes.

Summary

Developments in public health genomics (PHG) hold the promise to be beneficial for individuals and to promote public health. Central to this paper is the idea that given the range of uncertainties and ambiguities related to genome-based information and technologies (GBIT), the responsible introduction of GBIT in health care systems requires an incremental approach. The paper highlights policy issues connected to two major shifts connected to developments in PHG that challenge traditional boundaries. First, the introduction of GBIT in health care systems challenges the boundary between research and clinical care. It entails complex data flows that raise a number of issues relating to infrastructural demands, intellectual property, data security and privacy, tensions between the needs of research and the needs of the individual, patient rights and professional responsibilities, and the potential feedback of (re)analysed data. Secondly, the introduction of GBIT in health care systems challenges the boundary between clinical care (particularly diagnostics) and screening. Both diagnostics and screening involve potentially large amounts of information about an individual's genome, and raise new and challenging issues concerning quality assessment and how to deal with unsolicited information that might be generated from these tests. These issues could arise in a variety of health care settings in which whole genome sequencing tests find further application in established and new practices of diagnostics and screening. The possibility of screening the whole genome raises the question of what to screen for and when, and whether existing evaluative frameworks – concerning quality assessment and ethical and legal aspects of GBIT – are robust enough, or require fine-tuning. These shifts have implications for the relations between all stakeholders. The responsible introduction of GBIT in the health care system thus requires an early dialogue in which these stakeholders are actively involved.

1. Introduction: manifold uncertainties warrant incremental approach

This paper is part of the project *Future Panel on Public Health Genomics*, which aims to support an expert-based policy agenda for the future of public health genomics. The 'Future Panel' consists of parliamentarians from different European member states who have a special responsibility in this field.

At the start of the project, the Future Panel formulated a list of questions and issues they considered particularly relevant for setting a policy agenda for public health genomics. Four international Expert Working Groups (EWG) then issued reports focusing on: the state of human genome research and its perspectives for future medical applications in public health genomics (EWG1); issues of quality

assessment and regulation (EWG2); economic and societal issues (EWG3); and ethical, social and legal aspects of public health genomics (EWG4).[1]

The aim of this paper is to summarize the main findings of these reports in a way that will allow policy makers to consider major policy issues and options with regard to the future of public health genomics in the European Union and its member states.

1.1. Can the promises of public health genomics be fulfilled?

Issue raised by Future Panel:

- *How to avoid hypes, that is, how to discern hype from reality?*

With DNA-sequencing technologies rapidly becoming cheaper and faster, it is envisioned that we will soon be able to get a full human sequence within a day and for less than € 1,000. This will stimulate further application and greatly improve our understanding of the health status of our bodies and variations between individuals. Reduced sequencing costs are not only expected to stimulate the analysis of genomes of people with diseases, but of *healthy* genomes as well. Some experts expect that this will ultimately give us the tools to understand individual genomes and to accurately predict their consequences (EWG1: 1.4). Others believe that useful applications will be more limited.

The promise of new genome-based information and technologies (GBIT) is that at some point it will allow for detailed risk profiling, and will yield greatly improved health outcomes. Thus far, these promises have not been fulfilled. Opinions differ on the extent to which they will be realised in future.

- *A major challenge is that there is a wide gap between the ability to generate 'more data for less money', on the one hand, and the lack of understanding and validation of the clinical utility of these data, on the other (EWG1: 4.1, 4.3).*

There are two general responses to this. The first is that we must enhance our knowledge e.g. by doing more research, creating large biobanks and sharing the genomic data as widely as possible through a big data infrastructure (EWG1: chapters 1 and 2). A second response is to temper expectations somewhat. While genome-wide association (GWA) studies have identified hundreds of genetic variants associated with complex human diseases and traits, most variants identified so far confer relatively *small increments in risk* (EWG4: 2.1). Apart from monogenetic diseases, the 'causal' role of genomic variants in increasing or decreasing a person's susceptibility to common diseases is often minute. It has not been satisfactorily elucidated how such risk factors interact, and to what extent they depend on particular variables in our environment (EWG1: 3.3).

- *Both responses support the need for an incremental approach to the introduction of genome-based information and technologies in the health care system.*
- *Without robust databases that allow for an evidence-based/informed interpretation of normal and pathogenic genomic variants, there is a clear threat that a premature technology and market driven application of next generation sequencing (NGS) in clinical practice, will inundate physicians and patients with meaningless and/or uninterpretable data (EWG1: 4.1, 4.3).*

1.2. From roadmap to landscape

Some future visions of public health genomics (PHG) suggest a *paradigm shift* in health care towards personalized, predictive, preventive and participatory (P4) medicine. This notion of a paradigm shift is marked by uncertainties, ambivalences and controversies. An alternative view is that genomics will

[1] Appendix 1 gives an overview of members of all parties directly involved in the project.

provide clinical benefits in some areas, such as earlier diagnosis of genetic disorders and more targeted cancer treatments, whilst delivering little in terms of reliable, useful predictions of complex disease.

With this background we do not therefore see the future of public health genomics in terms of a 'roadmap' leading us in one particular direction, but rather as part of a 'landscape' where new technological developments may affect the current and diverse 'landscape' of health care in a variety of ways. In this process new options are created for diagnosis, treatment, screening and prevention. Each of these options will raise different issues that have to be considered in a way that allows experts, stakeholders and policy makers to gradually learn about and decide upon the future opportunities and societal impacts of public health genomics.

1.3. Outline

We will first discuss some general challenges that are raised by current developments in the field of human genome *research and innovation* (§2) and by the emergence of new forms of whole genome testing in practices of *clinical care and screening* as anticipated in future visions of public health genomics (§3). We will focus the discussion on two significant shifts that are visible in these developments and which challenge the traditional boundaries between *research* and *clinical care* and between *clinical care* and *screening*. A central ethical and legal issue concerns the different frameworks that govern 'locations' within the health care landscape; blurring boundaries between these domains may lead to tensions between ethical and legal frameworks.

In the remainder of the paper, we will discuss some of the implications of these developments for the governance of emerging developments in the field of public health genomics (§4). Traditionally, governments have had an important responsibility concerning *public health*. In the absence of political 'intervention' new GBITs will somehow find their way into the public health landscape, and may not just be beneficial, there might also be detrimental consequences. An important question, therefore, concerns the role of governments and other players in shaping the future of public health genomics in Europe.

2. Medical genomics research and innovation: from patient to sample donor?

Issues raised by Future Panel:

- *Where to put the money for research (how to set priorities)?*
- *How to integrate genomic knowledge with knowledge of lifestyle and environmental factors?*
- *What business and governance models are needed to cope with increasing costs of research and innovation in the genomics area?*

Potential applications of GBIT in emerging practices of public health genomics are based on developments in the field of medical genomics that are still mainly in the research phase. Most variation in our DNA has not yet been investigated and we cannot yet assign potential consequences to this variation for individual health and disease. In order to establish relationships between particular variants observed in DNA sequences and their consequences for common diseases, it would be necessary to combine clinical and genomic data from large numbers of individuals. However, the extent to which this will deliver health benefits is a matter of debate, which is also relevant to decisions about research priorities and resources for large-scale data collection and sharing.

- *Data sharing is considered a key policy issue in medical genomics research (EWG1: 1.2 and 1.4).*

- *Sharing data requires an infrastructure for automated data exchange in large-scale biobanks enabling the collection, analysis and integration of massive amounts of digitalized personal medical data (EWG1: 3.6; EWG2: 4.3).*

Emerging practices of PHG are thus dependent on increasing the quantity of data travelling between research and patient care whereby data collected for medical purposes, as part of the individual doctor-patient relationship, are shared for research purposes and statistical analysis. Interpretations of these data may later be fed back to individuals via health care providers (EWG4: 4.1). The complexity of these data flows raises several issues and concerns relating to infrastructural demands (§2.1), intellectual property (§2.2), data security (§2.3), tensions between the demands of this research agenda and the needs of the individual (§2.4), patient rights and professional responsibilities (§2.5), and the potential feedback of (re)analysed data (§2.6).

2.1. Infrastructural demands: issues of harmonization and governance

The challenge of data collection in medical genomics research is already beginning to be met by a series of biobanks that have been established throughout Europe. However, standardized databases of genomic variation and tools for the medically relevant interrogation of genomic sequence data are still fragmented and not harmonized (EWG1: 3.6). This raises the question as *to what extent there is a need to further consolidate and expand this infrastructure into an interoperable European network*. To this end, it will be necessary to harmonise protocols for data collection and handling and address cross-border issues associated with data sharing. Dependent on research priorities, it may be necessary not only to integrate the enormous range of relevant biological datasets but also to link them to contextual information on environmental variables, lifestyle, nutrition, etc. If this approach is taken, all these data will need to be stored and, most importantly, integrated, analysed and interpreted. Quality assurance and data security will be crucial issues to consider in this context (EWG4: 4.3).

- *Concerted efforts are needed to monitor the current development of databases of human genome variations and international networks.*
- *Depending on the need for data sharing, the possibilities of a European harmonization initiative aiming at shared standards and nomenclature as has previously been established for the quality standards of genetic testing services in Europe, might be considered* (EWG1: 4.7).

The infrastructural demands of large scale biomedical research also increasingly drive a collaborative approach across sectored boundaries as they depend on expensive equipment in specialist facilities, tissue and sample collections from large patient and citizen populations, and on elaborate data analysis and computational capacity that is out of reach of all but a very few individual institutions or companies. New funding mechanisms such as public private partnerships (PPP) and joint ventures between pharmaceutical and informatics companies and major charitable funders are becoming increasingly common. This evolution creates new demands for data sharing arrangements that are capable of crossing national and regional boundaries (EWG3: 2.2.1). Legislation governing this type of data exchange across national borders is not currently in place. Considerable differences with regard to implementation and enforcement of legal provisions exist even among countries of the European Union who have signed the data protection directive (EWG4: 4.2).

- *There is need for sustained political initiatives to develop an appropriate ethical and governance framework for data sharing across the EU and with other emerging players in China, India, Latin America and elsewhere* (EWG3: 2.2.1).

2.2. Intellectual property: a fresh look needed

Issue raised by Future Panel:

- *What is the legal status of genetic information?*

Questions concerning intellectual property (IP) and patents for genes, how it is decided what is worth patent protection, and what should be publicly available for use, might be considered *closed* in the EU since the related directives have been voted on. However, the diminishing cost of whole genome sequencing and the developments of tests incorporating information on many different genetic markers deserve a 'reopening of the box'. Sharing and applying whole genome data will be made immeasurably more complex if it is burdened by thickets of patents each claiming ownership of discrete elements of the genome. This will inevitably push up costs and impede the introduction of innovative applications of GBIT in the health care system to the potential detriment of patients and to health care systems. Across Europe, health care systems are struggling to meet the demands created by novel opportunities and rising patient expectations at a time when there is significant downward pressure on finances.

- *It is time for a fresh look in Europe at the way in which IP is generated, and the use that can be made of various IP tools such as patent pools, copyrighting and open source licensing to serve a range of societal and economic benefits* (EWG3: 2.2.3).

2.3. Big data: challenges for data security and privacy

Issue raised by Future Panel:

- *How to manage data in order to protect people?*

A new 'big data environment' is emerging from developments in medical genomics. This implies the implementation of procedures to guarantee the security of enormous quantities of highly sensitive data (EWG3: 4.4.1). In the context of research, special emphasis has been put on the need to make data and research results widely available to other researchers. Therefore databases have been elaborated requiring researchers to deposit anonymized data used for their publications, in order to enable the use of those data for further research. In endeavouring to balance respect for privacy and enable research, current debates focus on the elaboration of data sharing policies and the *limits of anonymization or de-identification* (EWG4: 3.4).

A major policy debate currently taking place in the EU is the development of the new Data Protection Regulation and the extent to which this should reduce or increase an individual's control over their health data and electronic medical records. Advocates of 'big data' (including many commercial actors) argue that current data protection legislation should be weakened to allow data mining of pseudo-anonymized health data and perhaps to exempt not only fully anonymized, but also pseudo-anonymized data from data protection and informed consent requirements altogether. However, many studies show that medical data cannot be effectively anonymized, especially once whole genomes are included (EWG4: 4.2). Even if healthcare and research infrastructures build robust strategies to provide maximum privacy protection, new privacy risks are developing with the increased availability of DNA ancestry and genealogical tests. Storage of genomes linked to other data also may allow third parties to track individuals and their relatives.

- *It is now widely regarded as misleading to promise privacy protection to research participants in whole genome studies (EWG4: 3.4).*
- *A main challenge arising from this security debate is how to foster in Europe the development of an appropriate common ethical framework that protects research participants and sample*

donors and allows for safe and secure data access for the research community, for participants, donors and the public (EWG1: 4.7).

2.4. Tension between the needs of research and the needs of the individual

In considering data sharing policies we should distinguish between two purposes for the storage of genomics data. First, the storage of aggregated and anonymized data from many individuals in order to generate new genome-based knowledge of possible future value for the community and the individual. Secondly, the storage of an individual's genomic data in order to prevent or manage disease on a personal basis. These two different purposes imply a tension between the needs at the level of research – widely sharing genome-based information as a basis for data integration – and the needs of the individual – only receiving specific genome-based information for specific purposes (EWG1: 2.5).

From the latter perspective, storing whole genome sequencing information as a standard means of health care might be seen as premature today. However, we can expect that in emerging practices of PHG, genomics data may more and more become part of the individual clinical record. While most clinical records are related to the current health and disease status of an individual, genomics data may contain information on health aspects that could affect current or future life, but that may not have any immediate consequences for his or her health. Therefore, if whole genome sequencing data become stored in individuals' records, the clinical access to these data will have to be delineated in layers related to the specific questions that may arise in the context of specific medical purposes along the life of the individual (EWG1: 2.6).

- *Research and patient care are shaped by different interests, objectives, duties, and rules. If procedures are set out which allow transfer of data from one context into the other they should pay attention to the specific rules and protections which guard the different domains.*

- *Since with GBIT based research the boundary between biomedical research and medical care becomes more and more permeable there is a need for harmonization of legislation governing the two domains.*

- *Building a future infrastructure for processing, storing and maintaining genomics data in a clinical context, will raise the question of how to limit access to only the genomic information that is needed at any one time, without the need to delete information of the individual which could be of use in future evaluations of his or her health* (EWG1: 2.6).

2.5. Patients' rights and professional responsibilities

Issues raised by Future Panel:
- *How should medical services be adapted to act as a legitimate interface between producers and consumers of genetic tests?*
- *Right-(not)-to-know*

Debates about how much information should be provided to individuals in the context of medical genomics research and emerging clinical practices of whole genome sequencing, revolve around the importance and meaning of *informed consent* as a fundamental patient right, which is tightly connected to the doctor-patient relationship. Data storage in large-scale biobanks poses challenges to traditional informed consent because data may be shared with large numbers of researchers, including commercial companies, both nationally and internationally, for purposes that may be unclear when the data sets are collected. Open sharing of data makes it difficult for physicians to

reliably inform their patients about how their data might be used and to provide guarantees about confidentiality (EWG4: 4.2).

Concepts such as 'presumed' consent and 'broad' consent have been introduced to fit the paradigm of data-driven research. Under a model of *broad consent*, individual participants delegate their decisions on what research is ethical or in the public interest to third parties or ethics committees. Various mechanisms have also been used to engage the public directly in decisions about biobanks, however such processes are always framed by assumptions that creating the biobank is a good use of resources and data-mining will serve the public good. In many cases it is unclear whether or how the public has a say in deciding what is in the public good. The concept of *presumed consent* differs from broad consent and is often thought to be more controversial, especially to the extent that it implies a shift from an 'opt-in' to an 'opt-out' approach to medical research in which data can be widely shared without the individual's knowledge or consent. That would remove people's choice to take part in some research projects but not others, based on their own views of the risks and benefits (EWG4: 4.2).

- *A relevant question in this regard is whether systems of presumed consent are necessarily at odds with the individual right to self-determination, or can be organized in such a way as to be compatible with it.*
- *Another important question which should be answered by qualified empirical research is what potential donors would want and whether there is a large support for either specific, broad or presumed consent in the population.*

In any case, options for 'presumed' or 'broad' consent to the indefinite storage and widespread sharing of genomics data for research seem difficult to reconcile with existing rulings for biometric databases. For example, the EU's Article 29 Data Protection Working Group states that a prerequisite to using biometrics is a clear definition of the purpose for which the biometric data are collected and processed, taking into account the risks for the protection of fundamental rights and freedoms of individuals. The Group states: "It must be clear that such consent cannot be obtained freely through mandatory acceptance of general terms and conditions, or through opt-out possibilities*"* (EWG4: 4.2).

- *Finding acceptable and workable approaches to informed consent can be seen as a major challenge for current 'big data' research in medical genomics and the future of PHG* (EWG4: 4.2).

2.6. Feedback of (re)analysed data?

A further set of issues relating to data sharing concerns the potential *feed-back* to individuals and their families of research findings produced by (re-)analysis and interpretation of sequence data that have been retrieved from a biobank to which these individuals have donated. For example, variants of unknown significance might suddenly turn out to be deleterious variants. To what extent should healthcare professionals be entitled to re-contact their patients? Does this belong to the physician's continuing duty of care? Should a physician be responsible for monitoring a patient's condition over a prolonged period of time? And how and when should a patient be re-contacted when new information becomes available? Is it an infringement of patient's privacy if patients are being re-contacted? Is it even logistically possible to put such a responsibility on healthcare institutions? (EWG4: 3.3 and 4.3).

- *How should the rights and duties of researchers, clinicians and individuals in relation to the validation and feedback of results (actionable or non-actionable) and the potential implications for an individual's care be defined and organized?*

- *One option is to give people a say about whether or not research findings will be fed back to them in the future* (EWG4: 4.3).

3. Introduction of GBIT in health care settings: from diagnosis to screening

Genomic tests are already routinely performed in a clinical context for diagnostic purposes using 'microarrays'. Such arrays may be used for the analysis of selected sections of a patient's genome, but also for *genome-wide* screening (WGS) focusing on structural variations that may explain particular conditions (EWG1: 1.3). Today, genome-wide microarrays are used for postnatal diagnosis in children born with congenital disabilities and/or mental retardation, with the aim of determining possible structural causes at the genomic level. Such arrays are also used in invasive prenatal diagnosis procedures to find the cause of fetal abnormalities observed during ultrasound (EWG2: 2.3). As available DNA-sequencing technologies are rapidly becoming cheaper and faster, it is expected that reading the full DNA sequence will more and more replace current array-based technologies. Thus it may become routine to sequence genes or even whole genomes of individuals for both diagnostic and screening purposes (EWG1: 1.3).

By providing a potentially large amount of information about an individual's genome, these tests raise new and challenging issues concerning the quality assessment of these tests (§3.1) and how to deal with unsolicited information that may be acquired from these tests (§3.2). These issues may arise in a variety of health care settings in which whole genome sequencing tests may find further application in established and new practices of screening. The possibility of screening the whole genome raises the question what to screen for and when (§§3.3-3.4). Issues of quality assessment are not limited to testing itself, however. Indeed the quality of genomic testing ultimately depends on the quality of the public and commercial laboratory and clinical services through which tests are provided (§3.5).

3.1. Challenges for the quality assessment of genome-wide tests

Issue raised by Future Panel:
- *How to define the validity and reliability of tests?*

An important issue to be considered in decisions about the introduction of genome-wide sequencing tests is their *diagnostic and predictive quality*. This involves an evaluation of a variety of aspects, including test performance and the benefits and potential adverse effects of testing. Several professional organizations and government-sponsored initiatives have developed guidelines for the evaluation of genetic tests. There is substantial agreement about the criteria that are considered of key importance. These criteria are generally referred to as *analytic validity*, *clinical validity* and *clinical utility*, which together with the ethical, legal and social implications form the core of the internationally established ACCE model. Whereas analytical and clinical validity refer to the diagnostic or predictive power of a test, clinical utility refers to the *usefulness* of the test information to medical practice and the individual receiving this information (EWG2: chapter 1).

A crucial difference between whole genome sequencing (WGS) and traditional monogenetic testing is that the results of one single WGS test can be used to inform an individual about a great variety of health risks. This will require a redefinition of what is considered a 'test' and will split the quality assessment in two parts. Whereas the technical quality of WGS is independent of the setting and purpose of testing, its *clinical validity and utility* are totally determined by the kind of health information that is derived from the test. In other words, the analytical validity of WGS can be established in a single assessment, but its clinical performance and usefulness have to be established in numerous assessments requiring different studies with different study populations.

- *If we want to help build the necessary evidence for the assessment of genomic tests, investments are needed in well-designed studies in populations that are representative for the intended health care applications of these tests.*
- *For the accumulation of evidence, multiple smaller studies tailored to the intended applications have more value than one analysis using data from a large, generalized biobank* (EWG2: 1.7; EWG1: 4.3).

The European Commission has recently funded The Public Health Genomics European Network (PHGEN II) project (2009-2012) with the aim of developing *European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies* and to support the member states to work together at a European level in addressing the challenges deriving from emerging genome-based information and technologies. Experts from across the field of PHG, representing key European and national organizations and institutions from policy making, academia and private sector, endorsed in 2012 a summary of the proposed 'European Best Practice Guidelines' in a Declaration of Rome. (EWG2: 3.5).

- *An important policy issue in this context is the funding gap that exists in the health care system. Research funding is available for the development of genomic knowledge and technologies, but is more difficult to find for the dedicated translational studies needed to establish the clinical validity and utility of tests* (EWG2: 2.5).

3.2. How to deal with unsolicited findings?

Issues raised by Future Panel:
- *Right-(not)-to-know*
- *How should the liabilities of various stakeholders be defined in case health decisions are taken that turn out to be wrong?*

Whole genome sequence data that are generated for a specific medical purpose in a clinical or research context may reveal unsolicited findings. They may be findings that have significant health or reproductive implications for the individual and/or their relatives, but also findings that are highly variable in their clinical manifestations or variants with unknown or no clinical significance. In medical genomics research, and emerging practices of PHG, professionals, institutional review boards, patients and their families will increasingly have to face the question of how to deal with these unsolicited findings (EWG1: 2.5; EWG2: 2.2). Thus, in a recent statement of the American College of Medical Genetics (2013), it is discussed as to what extent geneticists have a responsibility to disclose findings "that are not related to the indication for ordering the sequencing but that may nonetheless be of medical value or utility to the ordering physician and the patient". The question is currently part of an intense debate, in which some hold the position that unsolicited findings should not be reported until there is strong evidence of benefit, while others argue that in the context of PHG clinicians will tend to view unsolicited findings not as 'problems', but rather as 'opportunities' for individual patients and their relatives (EWG4: 3.3 and 6.6; EWG1: 3.3).

One strategy to overcome some of these problems is the use of filters to limit the amount of data and information generated, thus targeting a genomic test to a particular clinical purpose. The European Society of Human Genetics recently recommended targeting as much as possible. Furthermore, informed consent will have to be sought for the reporting of unsolicited findings. Thus, in addition to technical solutions, strategies of communication are being developed, providing informed consent documents to the tested individuals, explaining the unsolicited or unknown information that might become available and asking them to what extent they want to be informed (EWG2: 2.2; EWG4: 6.6).

- *It is important to distinguish between the analytic device which is used for a test (which could be whole genome sequencing or an array) and the specification of the sequences or genes which have to be analysed for a given purpose. Although the sequence of the whole genome may be obtained by such GBIT, only those genetic markers should be analysed and interpreted which are clinically validated.*

- *If analysis of only some genes or sequences is needed in order to answer a clinical question, the other parts of the genome should not be analysed (interpreted) in order not to create information which may not be validated or unsolicited findings.*

- *Crucial requirements for the introduction of genome-wide sequencing tests in health care settings are the development of targeted approaches of testing and appropriate strategies of informed consent. However, these two strategies will also need to be weighed against each other.*

3.3. Screening in early life

Issues raised by Future Panel:
- *What will the impact of genetics be on the health and health care experience of individuals?*
- *How will health costs evolve due to developments in genomics and increased use of applications?*

The introduction of genome-wide sequencing tests is currently being considered and debated for a number of established screening programs in the context of reproductive and newborn health care settings.

Pre-implantation genetic screening (PGS)

With the aim of improving the outcome of IVF procedures, pre-implantation genetic screening (PGS) for abnormal numbers of chromosomes (aneuploidy screening) in the embryo is routinely being performed, at least in some countries. The use of microarray technology is currently being evaluated to further improve the procedure that will also allow for the detection of other structural chromosomal defects. *Whole genome* sequencing of a pre-implantation embryo might provide the opportunity to perform a comprehensive chromosome screening and simultaneous analysis of single gene disorders. Although a growing amount of information may be helpful in selecting embryos with a good chance of implantation after IVF, it will also raise difficult questions for professionals and prospective parents.

- *Most probably every embryo will present with one or more recessive or disease causing mutations. Furthermore, many embryos contain one or more cells with abnormal chromosomes. On what basis will an embryo for transfer be selected and who is to decide? (EWG2: 2.4; EWG4: 2.3).*

Non-invasive prenatal testing

The introduction of non-invasive prenatal testing (NIPT) is being discussed at the moment as a replacement for established forms of prenatal aneuploidy screening (in particular for Down Syndrome). NIPT is a prenatal test based on the analysis of cell free fetal DNA present in the maternal circulation and has already been proven to be valid for particular diagnostic purposes. It is now also considered as a promising screening tool for certain chromosome abnormalities, potentially reaching a high level of clinical validity and utility compared to current methods of prenatal aneuploidy screening. Moreover, NIPT is being developed as a diagnostic test for monogenetic conditions (EWG2: 2.3). As soon as NIPT becomes widely available in a setting of routinely offered prenatal screening, it may also create future opportunities for the introduction of

more *genome-wide* forms of screening, based on microarrays or sequencing. This will raise new questions about *what genomic test information to offer in the context of reproductive choice*, questions that may also become more urgent as a result of commercial initiatives in offering NIPT.

- *An important concern in this context is to what extent informed decision-making is still possible in a prenatal care setting in which a growing number of disorders may be identified in the unborn child (EWG3: 1.2; EWG4: 2.3 and 6.9).*

Newborn screening

Newborn screening (NBS) programs have been established for many years. Clinical validity and utility have been shown, but NBS is not yet equally accepted and implemented at the European level (EWG2: 2.4). NBS programs in the EU currently aim to identify 1 to 30 treatable conditions, mostly by measuring metabolites and enzyme activity. In some programs, DNA testing is integrated as a final step for cystic fibrosis screening (EWG4: 6.7). In 2011, an EU expert opinion document was published describing in detail why, how, and for which conditions, screening should be implemented in European countries. Taking into account current developments in whole genome sequencing, targeted *genome-wide* screening (for a panel of well-chosen diseases) could be envisaged based on the criteria used or suggested today to develop a screening program (EWG2: 2.4).

- *As the range of conditions that are potentially screenable grows, including diseases with limited effective interventions, designing procedures for informed consent will become a complex task and this issue might turn out to be intractable.*
- *Providing sufficient information and support to make it possible for parents to opt out of learning about particular disease risks, will inevitably mean extra costs that will have to be explicitly modelled in the cost/benefit evaluations of NBS programs (EWG3: 4.1.3).*

If indeed a switch were to be made to genome-wide screening in NBS programs, one could think of the possibility of keeping the whole genome sequence of the newborn for future use, whereby the stored sequence information could be analyzed later in life for dealing with specific questions or as a result of new insights relating to individual health risks (EWG2: 2.4; EWG1: 2.5). However, this option would imply the storage of massive amounts of data, creating serious threats to privacy and confidentiality, and would infringe the child's future right to consent and self-determination. Moreover, the infrastructure needed for storing, securing and administrating individual genomic data would create a long lasting burden for the public health care system without knowing whether the data would ever be of use for the individuals analyzed or whether they would generate a return for public health.

- *Some experts consider storage of whole sequence information of newborns as premature today and would also not advise widening current NBS programs by whole genome sequencing (EWG4: 2.3).*
- *Other experts strongly support the established concept that in newborn screening only information should be gathered that is actionable and of clinical utility for the child.*

What to screen for and when?

Issues raised by Future Panel:

- *How far do we go in collecting and interpreting information?*
- *Right-(not)-to-know*

Options for the introduction of whole genome sequencing in established programs for reproductive and newborn screening are currently being considered and debated in the context of research. NIPT has been shown to be analytically and clinically valid in pregnancies at elevated risk for Down

Syndrome. However, large scale - preferably randomised controlled trials - are needed, to demonstrate its clinical validity in a prenatal screening programme, especially if applied to low-risk pregnant women. The analytical validity of genome-wide screening in newborns is established and, based on what is known today about newborn screening, the demonstration of clinical validity and utility will follow (EWG2: 2.5). Consequently, more and more opportunities may be created for 'genomic profiling' in early life, raising difficult questions of what and when to screen.

- *One of the core ethical questions in this context is whether genomic data ease the burden of decision making in the context of reproduction or, on the contrary, exacerbate it. Most likely, the latter will be the case due to the tremendous amount of information that needs to be taken into consideration and weighed.*

The question therefore is whether genomic profiling should be implemented routinely in early life health care settings and if so, how and under which circumstances it should be done. There are at least two main options to deal with these challenges.

- *One option consists in carrying out whole genome sequencing at birth, thus integrating it into newborn screening. The data can then be used when needed during life for various specific health purposes.*
- *Another option is to use whole genome sequencing only for specific purposes and only at times when it is indicated that the individual patient may benefit* (EWG4: 2.3).

Restricting the amount of generated data as much as possible to what is clinically valuable would not only ease the burden of information and consent for patients and doctors involved in such analyses, but also limit the production of unsolicited findings and problems associated with privacy and access (EWG4: 2.3).

In considering options for the introduction of genome-wide screening in early life health care settings, the issue is not only how the increasing complexity and amount of information yielded by these techniques will challenge the principle of reproductive autonomy, but also the right of the child to an 'open future'. This applies especially to minors; their right to privacy and to provide consent for themselves once they are adult has to be respected (EWG4: 2.3 and 7.7).

- *An important issue to consider in a reproductive and newborn screening context is the right of parents to make far-reaching decisions about full genome analysis for children without knowing the possible benefits of such an analysis at the time taken.*

There is broad consensus that in case of medical benefit, when a genetic test is likely to provide useful information for the medical management of the child, the test is either permissible or even obligatory. Whether or not this applies when there is no urgency in processing this information, because the condition might only develop later in life, is now under debate. Unnecessary psychological burden for the child and his family generated by the identification of mutations in a newborn that will not finally develop the disease (or develop a milder form) should be taken into account (EWG3: 4.1.3).

- *A major concern is that children, by genome-wide screening prenatally or at birth, will be deprived of opportunities later in life to make their own choices about whether or not to know.*

3.4. Screening later in life

Issue raised by Future Panel:

- *What will the impact of genetics be on the health and health care experience of individuals?*
- *How will health costs evolve due to developments in genomics and increased use of applications?*

The introduction of genome-wide sequencing tests is currently also being considered in the context of established or envisaged public health screening programs targeted at adult individuals, including *genetic carrier screening* and different forms of *cancer screening*. As the costs of whole genome sequencing continues to fall substantially, it is further expected that genome-wide sequencing tests will be offered more and more on a commercial basis by *direct-to-consumer genetic testing services*.

Genetic carrier screening

Recessive mutations can be identified in future parents through genetic carrier screening, thus allowing them to make informed reproductive choices which may prevent the birth of an affected child. There have already been for many years, public health programs which offer carrier screening for particular genetic conditions to communities in which these conditions are relatively prevalent, like thalassemia in Cyprus and Tay Sachs occurring in Ashkenazi Jews. Such programs are also advocated for other recessive conditions like cystic fibrosis. In this context it might be envisaged to apply *whole genome* sequencing in a targeted way, thus offering future parents the opportunity of screening for a range of relatively frequent as well as more rare recessive conditions. Another option that might be considered in this context is the combination of newborn screening at birth and carrier screening later in life by using the same sequence data at different time points.

- *Again, these options raise the question who should decide – and on the basis of what criteria – about these opportunities and the range of reproductive choices offered.*

Public health leadership might take responsibility for the implementation of these opportunities after a thorough ethical and health economic evaluation, but there is also the real possibility that commercial providers take the lead in offering these services on a commercial basis (EWG2: 2.4; EWG4: 6.10).

Cancer screening

DNA sequencing tools are already used today for the genetic profiling of tumours as a basis for more personalized treatments of cancer. Full DNA and RNA sequencing of cancers is expected as one of the first clinical applications of next generation sequencing technology aiming at targeted therapeutic interventions (EWG1: 3.3.3). Future impacts on health will depend on the extent to which new treatments can be developed based on this information. In addition to these promising diagnostic applications, sequencing tests are also being considered as a possible tool in developing stratified screening strategies for breast, colorectal and prostate cancer, based on multiple genetic risk factors. Such risk profiling strategies could potentially improve the efficiency of current and future screening programs and reduce their adverse consequences, although further research is needed to establish whether this is in fact the case (EWG2: 4.4). Cascade screening is debated as another potential strategy to target individuals who are at greater genetic risk for cancer. The starting point of this strategy is the testing of all patients for genetic risk factors on the basis of which family members can be informed if particular risk factors have been found. This strategy has been considered for example for Lynch syndrome, a relatively common hereditary form of colorectal cancer. Instead of using single genomic tests for different cancers, cascade screening might also be based on a *genome-wide* screening strategy to include in a more efficient way risk factors for a range of hereditary cancers. However, it is as yet unclear whether this would improve health outcomes in these high-risk families.

- *It is important to evaluate such comprehensive strategies not only in terms of the costs of screening, but also in terms of all the costs related to the circulation of sensitive genetic information between different health care services* (EWG3: 4.1.3).

Direct to consumer testing

Issue raised by Future Panel:

- *How to regulate direct-to-consumer markets?*

Private companies have established commercial services on the internet which offer direct-to consumer (DTC) genetic testing for susceptibility variants associated with common complex disorders (EWG2: 3.3). Many concerns have been raised with regard to the limited clinical utility of many of the tests being sold by these companies.

- *The marketing of these tests is generally seen as a premature development and companies have been criticized for overstating on their websites the predictive value and the potential health consequences of these tests.*
- *These criticisms and concerns have been further fuelled by the absence of genetic counselling when providing test results directly to consumers, and by the fact that various DTC companies don't follow clinical guidelines with regard to the testing of minors.*

Some DTC companies have started to suggest that consumers should contact a healthcare professional for further interpretation of their test results. As this does not dissipate the main concerns with regard to the quality and appropriateness of these tests, it may lead to a downstream impact on the publically funded healthcare system when consumers seek follow-up testing and examination in regular health care (EWG4: 5.1). However, it seems that consumer interest in commercially available genetic tests has remained low so far (EWG2: 3.3).

Several professional societies have developed recommendations related to the quality of DTC provision and issued statements identifying deficiencies in the regulatory framework (EWG2: 3.3). One issue of debate is focused on the way individuals can access genetic tests. Various EU member states (including Portugal, France and Germany) have introduced legislation that regulates the provision of genetic tests. The legislation in these countries has been strongly influenced by the Additional Protocol concerning genetic testing for health purposes that was approved by the Committee of Ministers of the Council of Europe.

- *Policy makers should decide to what extent genetic-specific legislation is necessary and the relevant articles from the Additional Protocol and the original Convention could be integrated in European or national legislation* (EWG4: 5.1).

Another issue of debate is focused on the regulation of genetic tests before market introduction. In the USA, the FDA has recently ordered the leading online gene testing company 23andMe to cease marketing, due to its failure to supply clinical data to support its claims. In the European framework, the regulation of genetic tests falls within the scope of the in vitro diagnostic medical devices (IVD) Directive. The European Commission has recently published a proposal for a revised IVD Regulation that is currently being discussed by the European Parliament (EWG4: 5.1). The latest draft of the IVD Regulation proposes a ban on DTC genetic tests and requires the involvement of genetic counsellors. Clinical utility data is required only for "companion diagnostics" (tests combined with drugs) and is not reviewed prior to marketing.

- *Stricter regulation might be needed to control societal health care costs, protect the consumer and allow commercial DNA testing at the same time.*
- *To reinforce the participatory role of the public, new public-private modes of interaction might be sought for the provision of genetic testing based on professionally accepted quality standards* (EWG2: 3.3).

3.5. Challenges for public health genomics service provision

Issues raised by Future Panel:

- *How should medical services be adapted to act as a legitimate interface between producers and consumers of genetic tests?*
- *How to make sure that both medical professionals and citizens obtain a sufficient level of literacy to make adequate health care decisions based on genetic/genomic information?*

The quality of genomic testing ultimately depends on the quality of the public and commercial laboratory and clinical services through which tests are provided. However, there are notable shortcomings in the current level of genetic service provision in Europe and in the context of emerging practices of PHG new challenges will arise for the organization and quality of service provision.

Although *quality standards* are well developed for molecular and cytogenetic testing services as well as for reproductive and newborn screening programs, it has been shown in a recent study that the quality of genetic testing varies widely between European laboratories. Few countries explicitly regulate genetic testing and counselling and quality assessment in clinical services is still developing. Publicly funded projects such as Eurogentest have developed quality assurance procedures for evaluating genetic testing laboratories, but these standards are voluntary.

- *Until the participation in QA schemes is made mandatory it is likely that coverage will be incomplete, leaving professionals unsure and patients vulnerable* (EWG3, 2.1 and 2.2).

Advances in PHG may shift the focus of public health from strategies to combat disease determinants that appeared to originate outside the body, to individual genetic factors modified by environmental exposure. Thus, improved understanding of the genetic basis for common, complex conditions including cancer, heart disease and diabetes, as well as advances in testing of genomic biomarkers, might increase the relevance of genetic services for the general population. A defining feature of future PHG service provision for common diseases is the *high level of data integration* that it would require, enabling the analysis of complex information from multiple – clinical, life style and environmental – data sources to support the health of citizens and populations (EWG2: 4.3). Moreover, in this scenario, the role of the physician may be radically different: i.e. to provide guidance, wisdom, experience and critical appraisal of information compiled by patients themselves from a wealth of web-based clinical and genomic information (EWG1: 3.5 and 3.6). Several models have been proposed for dealing with these new challenges in PHG, for supporting the development and implementation of new innovative modes of genomic services provision.

- *For several medical areas, multidisciplinary collaboration between geneticists and other specialists has been advocated. There will also be an increasing need for integration of genetic services directly into primary care* (EWG2: 3.5).

If whole genome sequencing becomes mainstream in medical practice, the volume of sequencing data generated for a single individual and the *wide range of findings from whole-genome sequencing* will raise critical questions about the return of results and their potential value for end-users (EWG4: 2.3). With advancing technology and the ability to screen populations for dozens or even hundreds of conditions in a single analysis, the notion of an 'effective and affordable intervention' might have to be reconsidered. The question that both health care providers and their clients will have to face in this context is not what *should* be tested, but rather what *should not* be tested.[2]

[2] Health Council of the Netherlands (2010). *The 'thousand-dollar genome': an ethical exploration*. Monitoring Report Ethics and Health, 2010/2. The Hague: Centre for Ethics and Health, 2010. Publication number Health Council of the Netherlands: 2010/15E. ISBN 978-90-78823-16-2.

- *Designing procedures for really informed consent will become more and more a highly demanding task, multiplying the requirements of shared-decision making and requiring the empowerment of both health professionals and citizens* (EWG3: 4.1.3; EWG2: 4.4).

European health systems are facing *increasing demand* for expansion of genetic testing and genetic services provision. In all countries, non-specialist health professionals are ill prepared to take advantage of genetic/genomic knowledge and lack the necessary skills to make effective use of the new technologies in their practice. Investment in the development of existing genetic services and educational activities for professionals and the lay public might substantially improve medical services and quality of life in patients and families with rare genetic diseases (EWG2: 3.2). Moreover, it can be expected that the prospect of effective and responsible translation of GBIT into health care and the potential for their effective use across disciplines and diseases will be severely hampered by the availability of only a small number of health professionals with expertise in genetics.

- *There is an urgent need to carefully consider the scope of education and training needs in genomic medicine, tailored to the specific work of each speciality and of primary care providers.*

- *This includes the engagement and participation of (lay) communities and community advocacy organizations (i.e. patient organizations) to address their knowledge needs* (EWG1: 4.5 and 4.7; EWG3: 3.0).

4. Governance issues in public health genomics

Issue raised by Future Panel:
- *How to balance individual and collective choices and benefits?*

Different practices in the health care landscape are regulated by (somewhat) different norms. For instance, in a *clinical* setting, the individual right to self-determination is typically regarded as decisive in determining whether a specific intervention (diagnostics, therapy) is performed or not. Autonomous individuals have the moral and legal right to refuse even life-saving treatment. This is understandable, especially since in a clinical setting the aims of a potential intervention are tightly connected to the health and wellbeing of that specific individual. Things are somewhat different in a *public health* setting. It is often very difficult, or even impossible, to predict which specific individuals will benefit from specific public health interventions. The 'prevention paradox' entails interventions that may have a great impact on public health, may actually have very little to offer to identifiable individuals. Since in a public health context the aim is not so much to protect or promote the health and/or wellbeing of identifiable individuals, but the health of an entire population, it is clear that individual self-determination cannot have the exact same normative standing in a public health setting as it does in a clinical setting. The choices that individuals make in this setting do not just have consequences for themselves, but for others as well.

It has been argued that the introduction of new forms of GBIT in the health care system could lead to two significant shifts; blurring boundaries between research and the clinic in which patients become sample donors (§2), and blurring boundaries between diagnostics and screening (§3). Both shifts involve the introduction of collective (public health) considerations into contexts that may primarily have been regulated by individual considerations, such as the individual right to self-determination. Therefore, both shifts raise important governance issues involving possible tensions between individual and collective considerations connected to the introduction of GBIT. More specifically, these shifts raise the question as to whether existing evaluative frameworks – concerning quality assessment and ethical and legal aspects of GBIT – are robust enough, or require fine-tuning (§4.1). A programmatic approach, based on the collective weighing of what is needed and what is utile will remain necessary (§4.2). This requires robust institutional arrangements for the

evaluation of GBIT in which Health Technology Assessment can play an important role (§4.3). It also raises questions about regulation of drug development (§4.4), and requires an early dialogue in which relevant stakeholders are actively involved (§4.5). Such a dialogue is particularly necessary because the introduction of GBIT in healthcare systems has implications for the relations between all stakeholders, and because of the need to re-examine existing evaluative frameworks.

4.1. Need for reflection on evaluative frameworks

If the introduction of GBIT entails blurring the boundaries between practices that are regulated by somewhat different norms, potential tensions between these norms are to be expected. Focussing on *quality assessment*, two perspectives can be distinguished. Firstly, by emphasizing the well-established and robust nature of current frameworks for quality assessment. This implies that current and future developments of genetics and genomics in the context of public health should be firmly governed and regulated by these established frameworks.

- *The main challenge is then how to organize the process of assessing new genetic and genomic tests in ways that satisfy established criteria and apply to a variety of contexts.*

The other perspective emphasizes the potentially disruptive and transforming character of current and future developments of genomics in the context of public health, implying the need to reconsider established frameworks for assessing the quality of GBIT.

- *The main challenge is then how to organize a process of transformation of public health, which involves innovative applications of genome-based information and technologies for prevention and early diagnosis of common disease, guided by new notions of 'personal utility', whereby the usefulness of GBIT is assessed in terms of characteristics of the specific health needs and preferences of individuals.*

Both perspectives imply an urgent need for arrangements, both on the national and European level, that support and shape processes of translation of GBIT in practices of (public) health care by organizing evidence-based forms of quality assessment. The same holds for developing an adequate ethical framework to assess the potential introduction of GBIT. Various models, guidelines and legislations are already available for traditional genetic testing services, which emphasize the importance of a reliable and valid test instrument and test process, the acceptability of the test to the target population, the focus on an important or significant health problem, a positive benefit-harm ratio, voluntary participation, and a justification within the healthcare budget. These criteria can also be applied to decisions about the introduction of GBIT in (public) health care.

- *However, further reflection on these criteria is needed. The guidance from these criteria probably needs to be fine-tuned to address the specific challenges arising from applications of GBIT, such as: (a) data and privacy protection of whole genome sequencing data; (b) the potential availability of unsolicited findings from these data; (c) assurance of robust informed consent about 'what to know' and 'what not to know' (EWG4: 4.6).*
- *An important future challenge is the inclusion of GBIT in more comprehensive practices of data integration, including high-quality evidence from non-genomic data, which seems to be crucial to ensure a sustainable implementation of GBIT in public health practice (EWG2: 4.1).*
- *A central element in the discussion about evaluative frameworks is the exact scope of individual self-determination in the context of public health genomics, especially since the information generated by genomic technology may have implications for others as well.*

4.2. The need for a programmatic approach

Issue raised by Future Panel:

- *How will health costs evolve due to developments in genomics and increased use of applications?*

Governments have traditionally had an important responsibility for protecting/promoting public health. Public health is 'public' in the sense that it refers to the health of a *population*, but it also entails 'public' ways of protecting/promoting the health of a population; it stimulates *programmes* in which many individuals cooperate to produce goods that are not just private goods but public goods that could benefit everyone.[3] Producing such goods requires a 'programmatic approach', specifically a certain level of coordination guided by collective values (such as 'public health'). Part of the responsibility of governments is to formulate standards for such programmes.

According to the aims of PHG, the introduction of GBIT should be guided by criteria that assure a process of *responsible and effective translation* of medical genomics research and innovation into a variety of health care settings (EWG2: 2.5). Although it is generally expected that whole genome sequencing will become increasingly accessible to health care providers and consumers due to its decreasing price, the downstream costs of genome-wide tests might largely outweigh the cost of the sequencing, due to the large amount of information generated and the cost of analysis, the cost of counselling, the cost of false positives and negatives (and their medical consequences), etc. In the absence of political 'intervention' new GBITs will somehow find their way into the public health landscape, and may not just be beneficial but can potentially have detrimental consequences as well.

- *It is important that the availability of genomic tests in (public) health care practices is based on an appropriate evaluation of their clinical utility, and not only on the basis of technological availability* (EWG4: 3.5).
- *A pressing issue in this respect is whether the need for a programmatic approach in public health sets limits to introducing GBIT via other institutional arrangements, such as direct to consumer testing.*

Genetic services may cause considerable downstream costs which may deplete health care systems from money urgently needed to treat acutely ill patients. Such costs will be caused not only for measures necessary for data handling, storage and security, but also for interventions aiming at the prevention of disease in individuals carrying genetic risk factors which may or may not develop due to the statistical nature of such risks.

- *It should be made sure by the health care system that such measures will only be considered if there is a clear public health benefit.*

4.3. The role of Health Technology Assessment in the governance of translating GBIT

In order to help health care policy makers, health care providers and other relevant stakeholders to make informed – and country specific – decisions for the application of GBIT in (public) health care and to allocate adequate resources, the role of *health technology assessment* is vital (EWG1: 4.7; EWG2: 2.5). Health Technology Assessment (HTA) can be defined as a multidisciplinary process that summarises information about the medical, social, organizational, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased and robust manner. Its aim is to inform the formulation of safe and effective health policies that are patient focused and based on existing evaluation methods and best practices for clinical utility. However, *HTA is not*

[3] Verweij, M. & A. Dawson (2009). 'The Meaning of "Public" in "Public Health"'. In: Dawson, A. & M. Verweij (eds.). *Ethics, Prevention, and Public Health.* Oxford: Oxford University Press, pp. 13-29.

spread all over Europe. Some countries lack the expertise, while in others it is only supported by academia and not embedded in decision-making on health care provision. The need for homogeneous quality assessment processes in EU countries has been pointed out in several recently published documents and directives (Directive 2011/24/EU) and there are initiatives in place to establish a permanent network on HTA in Europe (EUnetHTA). The implementation of a network at the pan-European level and the establishment of HTA national/local initiatives will reduce the likelihood of introducing genomic technologies that do not comply with established quality criteria and the organizational, economic and managerial capacity to provide these services (EWG2: 4.4).

- *In this context, it is important to consider how to support HTA practices that are required for the assessment of clinical validity and utility of GBIT in agreement with previously described best practices and context based affordability along Europe* (EWG2: 4.6).

4.4. Regulatory challenges arising from the move to personalised medicines

Biomedical research is taking therapy development away from the traditional model of 'small molecules and big populations' to one of 'big molecules (up to and including genes, cells, etc.) and smaller populations'. This trend is also visible in the development of drugs that rely on the genomic characterization of patients and thus imply a segmentation of the market. A common disorder is broken down into a certain number of rare disorders. The number of patients corresponding to each subdivision of the disease may be relatively low, reducing the potential economic interest for drug makers (EWG3: 2.2.2 and 5.1.1).

- *The current pharmaceutical 'business model' will have to adapt to personalised approaches based on genomics and, at the regulatory level, possible changes in drugs marketing approval and medical devices directives in Europe need to be explored* (EWG1: 3.3; EWG2: 4.6).

There is a concern that the costs of compliance with the current regulatory system are in danger of imposing a crippling burden that will stifle innovation, which may lead to persistent unmet patient need and damage to the economic competitiveness of the EU. The pharmaceutical industry is currently lobbying to change the rules applicable for drug access to the market and for new forms of public private partnership in drug development. Their objective is a reduction in drug development costs and the maintaining of high profitability in the sector (EWG3: 5.1.1).

One possible alternative drug development model has become known as *Adaptive Learning* or *Progressive Marketing Authorisation*. This scheme proposes that phase 1 and 2 of a drug's clinical trials be collapsed together, and if successful, the drug is then moved to real world use with a structure and robust process of data collection following a modified phase 4/pharmacovigilence programme. This would shorten the development time to marketing authorisation and potentially reduce costs significantly, but could also increase risks for patients due to reduced requirements for pre-market testing. In parallel with this evolution of the regulatory framework, HTA will need to be able to establish the real value of innovative medicines for the patient, for society, and also for the health care system responsible for the patient hoping to benefit from a given innovation.

- *Central to the creation of a new regulatory framework is securing patient engagement in the process* (EWG3: 5.1.1).

4.5. Need for stakeholder involvement and early dialogue

Many individuals and patients have participated or are currently participating in genome sequencing projects worldwide. Researchers and physicians have a special collective obligation and responsibility to ensure the safety of this public trust. Finding a balanced approach that respects and protects autonomous decision-making, confidentiality and privacy and acknowledges family and

community interests, may require the engagement of key stakeholders in order to develop informed recommendations for how to integrate the new technologies for both the benefit of the individual patient and family/community/society.

- *It is essential to engage in policy discussion and in collaborative decision-making processes that involve relevant stakeholders, including patient advocating groups and civil groups concerned with issues raised by whole genome sequencing* (EWG1: 4.6 and 4.7).

5. Conclusions: from policy issues to policy options

Developments in public health genomics (PHG) hold the promise to be beneficial for individuals and to promote public health. Central to this paper has been the idea that, given a range of uncertainties and ambiguities related to genome-based information and technologies (GBIT), the responsible introduction of GBIT in health care systems requires an incremental approach. The paper highlights a number of policy issues connected to two major shifts that may result from the introduction of GBIT in the health care system: the blurring of the boundary between research and clinical care, and the blurring of the boundary between clinical care (particularly diagnostics) and screening.

The aim of this paper has been to summarize the main findings of several expert working group reports in a way that allows policy makers to consider major policy issues and options with regard to the future of public health genomics in the European Union and its member states. More specifically, the challenge is how to translate the policy *issues* that have been highlighted in this paper into policy *options* that will give content to an incremental and programmatic approach to the introduction of GBIT in health care systems. Part of this challenge will be to determine the exact role of politics/governments in the process of a responsible introduction of GBIT in health care systems.

Appendix 1

The Future Panel on Public Health Genomics

Involved from the start of the project:

- Maria De Belém Roseira (MP, Partido Socialista, Portugal)
- Yvonne Gilli (MP, Grüne Partei der Schweiz, Switzerland)
- Jens Henrik Thulesen Dahl (MP, Dansk Folkeparti, Denmark)

Joined the Future Panel at a later stage:

- Vittorio Prodi (MEP, Progressive Alliance of Socialists and Democrats, Italy)

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