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Table of contents

Preface

The contents of this report have been produced in a process of expert consultation that was part of a European *Future Panel project on public health genomics*. The overall aim of this project was to support policy making on public health genomics, and to create a mutual learning process between experts on the one hand, and parliamentarians and policy makers on the other hand. The Future Panel process was organized as a demonstration project within the framework of the European FP7 project *Parliaments and Civil Society in Technology Assessment* (PACITA).

The Future Panel consisted of parliamentarians from different European countries who were invited to identify major policy questions relating to the future prospects of public health genomics. These policy questions were the starting point for a consultation process, bringing together four Expert Working Groups who were asked to cover these questions in reports focusing on different themes. This document collates the four Expert Working Group reports. On the basis of this report an *Expert Paper* has been produced with a focus on policy issues raised by developments in public health genomics. Finally, policy options for dealing with these issues have been described in a *Policy Brief* that was discussed in a Policy Hearing involving the Future Panel and a variety of experts (Lisbon , January 2014).

Public health genomics is defined as the responsible and effective *translation of genome-based information and technologies* for the benefit of population health. In this report the prospects for and implications of this process of translation are discussed from four different points of view. Part I discusses the state-of-the-art and future of public health genomics, part II discusses issues of quality assessment and implementation, parts III and IV discuss the economic, ethical, social and legal aspects of public health genomics. Together these studies have offered a highly valuable input in the Future Panel project. Although the project has come to an end, we are confident that this report will continue to stimulate further debate about the future of public health genomics.

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Part I

The state of human genome research and its perspectives for future medical applications with Public Health Genomics

Report of Expert Working Group 1

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1 The book of our life in our handheld

Johan T. den Dunnen

1.1 Introduction

DNA is the basis of all life on earth, including human life. The methodologies for reading the DNA sequence - to unravel the code of life - are currently undergoing revolutions in both speed and cost. Nowdays it takes roughly 2-4 weeks to read the full DNA of a human and it costs somewhere between 2,000-5,000 Euros. The expectation is that in the near future (less than 5 years), the same can be done in 1-2 days and for considerably less than 1,000 Euros. This will have a significant impact on our lives with two major consequences. First, medicine will become genome-based, i.e. treatment will be based on the knowledge of our DNA, our building plan; personalized medicine. Second, when and if we want this knowledge, our DNA could be used to reveal the strong and weak points of our body, our talents and any hidden risks including genetic diseases. Although we are still in the early days of understanding the genetic code, serious progress is made every day especially regarding disease-associated DNA variants. Yet it is difficult to predict how much our lives will by driven by our DNA in the end. From what we know already, it will be a combination of our DNA (our genes), our environment, and how we live.

The aim of this chapter is two-fold. First, to describe the state of the art of genome-based technology (1.2) and discuss its most important applications (1.3). Second, to consider some of the expected future developments and to highlight one policy issue connected to the (potential) applications of these technologies (1.4) considered to be crucial: finding effective ways to share genomic data.

1.2 Technology - state of the art

The technology to read DNA sequences currently stands at a point where it takes 2-4 weeks to read the full DNA code of a human at a cost of 2,000-5,000 Euros. According to industry claims, the latest technology can achieve this in a day for a cost of 1,000 Euros (chemical cost only). Undoubtedly further technical developments will bring the time required down even further, probably to a few hours and to a cost way below 1,000 euros.

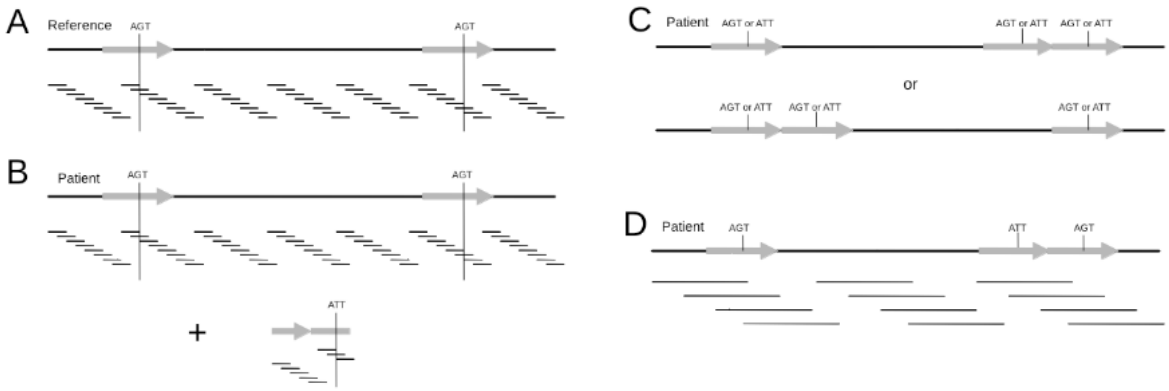
1.2.1 Reading the DNA

To read the DNA we have first to break it into millions of pieces (Fig.1). From each piece we then read 100 letters. Next we compare these millions of 100-letter fragments with a master, the reference human genome, and determine from which part each is derived. We gather up all the pieces and check whether the sequence is identical to the reference or contains variants. Finally, all variants found are listed and we evaluate their consequences, as far as is known or predictable.

The current standard for a *complete* human DNA is ˜100 Gb of sequence, i.e. to read each of the 3,200,000,000 (3.2 billion) letters 30 times or more. This 30-fold coverage is required to ensure, given random chance, that we have seen every letter of each of our 2 chromosomes (1 inherited from father, 1 from mother) sufficient times to be sure about its identity, being an A, G, C or T. When overall sequence cost drops we will undoubtedly go for even higher coverage, increasing overall certainty. Currently a human DNA sequence derived from 100 GB of sequence is roughly 95% complete and 99.9% correct. Most uncertainties do not derive from the sequence itself but from the complex structure of our DNA (Fig.1). First, some regions of our DNA are rather difficult to read, e.g. regions that contain high numbers of only GC or only AT letters. Second, some regions in our DNA are present in multiple copies (sometimes up to thousands of copies) making it difficult to impossible to determine where a particular 100-letter piece belongs. When we encounter a sequence difference in a repeated sequence, we cannot determine from which copy this difference came. Third, some

regions contain very long stretches of simple DNA sequences repeated thousands of times making a detailed analysis impossible. Technically, generating longer DNA reads (nowadays ˜100 letters long) will be instrumental to solve these problems. It should be noted, however, that with some exceptions, the segments of our genome that are difficult to analyse do usually not contain many genes of high interest.

Figure 1
A specific piece of DNA has the structure given in **A** (*Reference*). The sequence contains one piece of DNA twice (*grey arrow*) with at a certain position the sequence '*ACT*'. To read the sequence we first break it into pieces (*small lines*) and then read the sequence of each piece. After sequencing we compare each read and try to map it back to the reference. When the sequence is identical to the reference, each piece will fit (**A**). Sequencing of a patient (**B**) gives a perfect match with the reference but some pieces are left. These pieces indicate first that at the position of sequence '*ACT*' we also find sequence '*ATT*'. In addition we find new sequences that indicate we have a third copy of the grey arrow, located directly flanking one of the first copies (head-to-tail). Since we do not know which of the grey arrows is doubled nor know which of the copies contains the sequence '*ATT*' we have 6 possible options (**C**). When we would be able to read much bigger pieces it would not be a problem to determine the exact structure (**D**).



1.2.2 Listing variants and consequences
Although some technical problems remain, current technology does allow us to perform a detailed analysis for most of the important parts of our DNA (most genes) and to detect whether these segments contain differences when compared to reference DNA. The main problem of the methodology resides in the last step in interpreting the results. When differences in the sequences are found, what will their consequences be, if any? For a number of genes (˜3000), past analysis has shown what functions they have in our body and when defective, what the consequences can be. These consequences range from serious, sometimes lethal, health problems (genetic disease), to increased risks for specific diseases (e.g. cancer predisposition), to specific characteristics (traits), to our blood group, skin and eye colour, to having no effect at all. In general, one DNA variant is rarely directly responsible for one specific characteristic. The rule is that one DNA variant, in combination with others and the influence of the environment, gives an increased or decreased risk.

In DNA diagnostics we aim to report all variants found and the associated consequences. Our knowledge is based on 3 main elements: (i) the individual and their family; when a variant is associated with a consequence it should segregate in the family. (ii) Laboratory tests performed to determine possible functional differences between the normal and the variant sequence. (iii) Shared knowledge where we report worldwide what we encounter; which variant has under what

circumstances which consequences. Great certainty can only be given when a variant has been encountered in several unrelated families, always with the same consequences and when functional tests support the effects of the variants. Driven largely by studies to unravel the cause of genetic disease, many DNA variants could be linked to specific genes at the same time highlighting the function of these genes. Such findings are shared through publication giving others the option to perform similar studies and strengthening the initial findings. Recently, genome wide association studies (GWAS) were used to link regions in our genome to phenotypes like blood pressure, lipid levels, diabetes, etc. The links found here are indirect associations, i.e. the DNA variant tested is not causative but another variant somewhere nearby. Additional, often extensive, research is then needed to identify the true 'causal' variant, the DNA letter that is directly responsible for the feature studied.

Unfortunately a lot of what we learn from genetic studies is neither published nor shared, and is therefore lost. In addition, most variation in our DNA and many phenotypic characteristics have not yet been investigated and we cannot yet assign potential consequence to them. When we find DNA variants for which no consequences are known or for which no studies have yet been performed, we use a computer to predict, based on our current overall knowledge, what the consequences might be. Depending on the variant and its location in our DNA, the reliability of these predictions can vary from 'very reliable' to 'good guess'. In the end, only additional cases (families) with the same combination of variant and consequence or direct laboratory experiments can give the true answer. While the latter is time-consuming and costly, establishing effective ways of sharing all we know seems simpler and more cost-effective (see Chapter 2).

1.3 Applications

Below are a few examples of the application of reading DNA sequences with a focus on their current possibilities and their strong and weak points. It should be noted that the age of an individual at which the analysis is done does not mean a change in the technology used. It can be applied at any age, in adulthood, for newborns, prenatally or even pre-implantation. Tests can be performed to analyse all DNA (whole genome sequencing - WGS, looking at everything); to analyse the genes only (whole exome sequencing - WES, looking at 22,500 genes); focused targeting of sets of genes of specific interest (e.g. analysing only genes known to be involved in deafness); or a single gene or nucleotide (e.g. testing for Factor V Leiden). While these tests use the same technology to read the DNA sequence, sample preparation will largely differ, enriching the DNA of interest before sequencing is performed. The main reason to perform a focused analysis or simpler assay is cost - *it is cheaper to analyse less*. An additional reason can be that one wants a simple answer and less chance of 'unsolicited findings' (finding things one was not looking for).

While the cost of reading the DNA is dropping steeply, the cost of preparing the sample and selecting regions of interest, is not. Whole genome sequencing can be used as a substitute for any of the targeted approaches using a simple computational trick, i.e. analysing the regions, genes or nucleotides of interest only and computationally masking the rest. So WGS can be used to generate a WES or even an array-based result (e.g. a SNP-array). Any subsequent interest in other regions/sequences simply means modifying the computational analysis; no new data need to be generated and cost is negligible. At some point sequencing everything will be cheaper than performing targeted assays.

Compared to sequencing, (micro-) array technology uses the same sample from an individual but a different technology to read the result. While sequencing reveals every DNA sequence in the sample, an array is a highly focused technology answering only the question 'is this piece of sequence present in the sample'. The design of the array determines the tests performed. One application used frequently in DNA diagnostics is an array used to determine whether sequences in a genome are

present in normal amounts (CNV tests, copy number variation). Deviations show which sequences are absent (deleted) or present too much (duplicated or amplified).

1.3.1 Non-invasive prenatal testing (NIPT)

To test whether a fetus is affected by a genetic disease (prenatal diagnosis), we currently rely on fetal material obtained from amniotic fluid or chorionic villi. To obtain this material we have to perform an invasive test with a small risk (below 1%) of spontaneous abortion. It has been shown that the blood of a pregnant female contains free-floating DNA, some of which is coming from the fetus (up to 5%). Although it is not simple to recognize or analyse this fetal DNA in the >95% maternal DNA, it is possible. A first application is a brute force method that reads the DNA of 5-10 million pieces. From each piece we then determine from which chromosome it derived and we do total counts per chromosome. When more reads then expected come from 1 particular chromosome it indicates the fetus carries a numerical chromosome aberration. The best known example is three copies of chromosome 21, Down's syndrome. This simple but effective test is currently applied in a diagnostic setting in several countries. When the cost of reading DNA drops, new applications will emerge which will require many more than 10 million reads to be conclusive.

1.3.2 Genetic disease, rare disease

Currently (for financial reasons), whole exome sequencing (WES) is the technology used most frequently to study the cause of unknown genetic disease. Roughly, WES yields the answer in a third of cases and in a third of cases it yields a likely cause (awaiting further experiments or data from similar patients). In the remaining third of cases we remain in doubt; we may have possible variants but the evidence is too low to justify further work. Given the rarity of the diseases we study using WES, sharing data in an earlier stage seems the way forward to improve our success rate (see Chapter 2). Another reason why not all cases can be resolved is of course the fact that by using WES we only analyse ˜2% of all DNA. The cause might be in pieces of DNA we did not analyse or, since the technology is not perfect, some genes might have been below the quality thresholds we set (e.g. not sufficient coverage to allow a reliable variant calling). Overall, while not perfect or successful in all cases, WES is currently the technology that enables the biggest step forward in understanding our DNA and all our genes. At the same time it provides many patients/families with an answer to the cause of their health problems. Given the limitations of WES (i.e. not all DNA is checked) it will be replaced with a full DNA analysis as soon as finances allow.

1.3.3 Cancer

DNA sequencing has been used extensively to analyse cancers. What is evident from these studies is that although some common themes exist for specific cancer types, every cancer is different. As a consequence, every cancer will require a different treatment to increase the chances of success (personalized medicine). Besides the analysis of the cancer DNA, a cheaper alternative is the analysis of RNA (i.e. the message from the DNA, the genes, carrying the information for the body to make all proteins). The information sequence analysis given is currently beyond what we can interpret, yet our knowledge is rapidly growing. Some specific successes have been achieved where existing drugs have been used for the effective treatment of some forms of cancer. Full DNA and RNA sequencing of cancers is expected as one of the first applications of NGS (Next Generation Sequencing) technology.

1.3.4 Pharmacogenomics

There are large differences between individuals regarding how their bodies deal with (‘metabolize’) drugs and adverse drug effect is currently a significant factor in overall medical cost. A range of DNA variants have been identified that determine how a body metabolizes specific drugs and the best dosage on which to start treatment (lower/higher), or which drugs should not be given at all. With increasing knowledge of these factors and dropping costs, sequencing will become an important and effective tool. Together with all the other knowledge gained from a person's DNA, and the associated

long-term cost savings achieved, these pharmacogenomic aspects may be one of the drivers to offer full DNA analysis of an individual before any treatment is given or even before any disease is apparent.

1.3.5 Transcription sequencing

While the DNA sequence sets the basis, RNA can be used to 'see what's happening'. First examples showed how the regular sequencing of RNA from a blood sample could be successfully used to monitor the health of an individual. Besides confirming what can be seen from the outside, the strength of such analysis is that the early signs of upcoming disturbances can be detected; a viral infection can be seen days before the individual gets a fever and becomes sick. As technology costs drop, it can be predicted that regular sequencing of blood-derived RNA will be used to monitor health, especially when the early signs of a disturbance can be used for preventive treatment.

1.3.6 Non-medical testing

People have always been interested in where they came from, who their ancestors were and where they lived. Together with the growing knowledge about what our genome can tell us about ourselves, companies have started to offer all kinds of direct-to-consumer genetic tests. Mostly these tests are not disease-related but they focus on nice-to-know aspects about our ancestry and heritage, so things like skin type (including advice about sunbathing) and choosing a partner. Dropping sequencing costs will bring reading the full DNA sequence into the affordable range and soon companies will start to offer such tests outside the medical field. A wealth of knowledge will be gained by such tests, including health related findings.

1.4 Future developments and policy issues

The expectation is that sequencing technology will develop further. The sequence reads will become longer (from 100 letters to thousands), we will get more letters from one experiment, so obtaining the data will become both faster and cheaper. This will be achieved by developing technologies that will perform single-molecule sequencing (virtually no sample preparation) and that will read the sequence electronically (i.e. label-free, no costly imaging). We will be able to get a full human sequence within a day and at a cost of well below 1,000 euros. This will stimulate further application but the main outcome will be a significantly improved understanding of our genome, the status of our bodies (1.3.5 transcription sequencing), and the variations found between individuals. Since the focus so far has been almost exclusively on understanding disease, reduced sequencing cost will stimulate the analysis of healthy genomes and it can be expected that we will learn a lot from these. Gradually we will build up evidence of all DNA variants encountered and connect these to phenotypic features. Substantial future developments should be expected from these trends, ultimately giving us the tools to understand a genome and accurately predict their consequences.

As indicated, a lot of what we learn from genetic studies is neither published nor shared, and is therefore lost. However, we can only learn from DNA sequences, the variants observed between individuals and their consequences, if we find effective ways to share data. Indeed, data sharing is a key policy issue for successfully translating genome-based technology from research to the clinic.

2 Population versus individual genomics data

Xavier Estivill

2.1 Introduction

Individuals show a great genomic variability, which translates into different features with respect to health and disease. Genome-based information, then, has an enormous potential to promote the health of individuals as well as populations (2.2). Actually, since individuals show a great variability with respect to health and disease, genome-based information and technologies will lead to a reclassification of phenotypes and disease in accelerating progress in biomedicine (2.3). The complete evaluation of the genomic features needs of comparison of data amongst many subjects, as well as the evaluation of the various layers of genomics knowledge (2.4). Progress in this information reveals a potential tension between the individual perspective and the population standpoint in public health genomics. From the population perspective, producing and sharing as much genomic information about individuals as possible, is to be preferred. From the individual angle, however, although beneficial at the level of each person, it raises several concerns, e.g. security, privacy and accessibility of the data (2.5). It may be technically possible to deal with this conflict, by creating 'layers of public use and individual value' of genomic data, which could be analysed with newly developed bioinformatics at different time points (2.6).

2.2 Storage of personal and population genomics data

Different types of genomic data are being produced from *thousands of individuals*, as a result of targeted or whole genome sequence analysis and other types of genomic studies, using high-throughput sequencing and genotyping technologies (Shendure et al 2012). There is an exponential growth in the production of genomics data, mainly as a result of research projects that target cohorts of patients affected by specific disorders (Rung and Brazma 2013). Due to their enormous value, the results of genomic research, even at these initial stages, are already being applied to specific areas of health. In the next few years we are going to witness an explosion of genomic tests, and they will become part of most routine medical exams at all levels. Despite the framework in which genome data is generated (large research projects of many individuals, targeted studies of few subjects, or individual analysis for screening or diagnostic purposes), genomics data stored from each subject has an enormous *value for both the individual and the community*.

The individual and community utility of the data generated by genomic analyses is constantly expanding. Individual genomic data has a clear utility for each subject, but the genetic information generated from hundreds of subjects in different clinical and exposure conditions (www.uk10k.org; www.1000genomes.org; www.twinsuk.ac.uk; icgc.org; www.irdirc.org) also has an enormous value for each individual. As a consequence, the variability of the genome of each individual can be correlated with the phenotypic characteristics of each subject, especially with respect to dysfunction of specific organs and systems, and in different life conditions. Conversely, the complete exploitation of the data cannot be achieved without the comprehensive view of the variability of the *genomes of many individuals of different populations*. Thus, the dissection of the different phenotypes of the individuals and the comparison of genomic features along many subjects is needed in order to evaluate the functional significance of genomics variability with respect to health and disease. The translation of the genomic knowledge will only be possible in the context of sharing data for the mutual benefit of the individual and the community (Ball et al 2012).

Storage of individual and of population combined genomics data is needed to completely understand the physiology and pathology of humans (Church et al 2012). Data files that contain the minimum information of each individual genome can be stored in manageable file sizes, but the cumulate

amount of data is growing at a very rapid pace. A whole genome sequence (a diploid genome) can be stored in full as a single text file of ≈6 GB, whilst a minimal genome containing the 'specific' variants of each individual might require only ≈60 MB. However, at the current stage of sequence analysis and interpretation, large files are needed, containing raw data amenable for further analysis with constantly evolving bioinformatics tools.

2.3 Phenotypes and new taxonomy of disease based on genomics knowledge

Genetic variation is an important contributor to human health and physiology. Knowledge of how genetic factors contribute to disease is crucial for *understanding disease risk*. The genomic information produced at the level of the analysis of hundreds of thousands of individuals will rapidly accelerate biomedical progress. Thus, it will be possible to integrate clinical with genomic information and dissect the genetic component of inherited disorders, cancer, infectious diseases, and response to drugs. This integration will eventually lead to new classifications of diseases.

On average, the genome of any individual contains *around 3-4 million sequence variants*, which can be classified into three groups: a) variants that have no effect (i.e. neutral variation); b) variants with an effect on the normal phenotype (e.g. height and eye colour); and c) variants or mutations that either cause or predispose to disease. Thus, at the phenotypic level, genetic variants will have no known association with disease, have either a clear clinical interpretation, or might be associated with disease but with unknown clinical significance.

Progress in the identification of genes and mutations have been enormous for *Mendelian disorders*, which have a strong heritable component, with mutations in single genes, inherited in either a dominant, recessive, or sex-linked fashion. More than 4,000 known Mendelian disorders are known and the genes involved in many other diseases (likely to be more than 3,000) will be determined in the next years (www.irdirc.org). While some inherited diseases have well defined phenotypes, others vary enormously in their clinical characteristics due to genetic heterogeneity and modifier genes.

Many disorders show genetic heterogeneity, with multiple mutations within a single gene or mutations across hundreds of individual genes. In many cases, they may be described as single gene subsets of *complex diseases* (Robinson and Mundlos 2010). It is expected that the proportion of common diseases explained by many rare, highly penetrant mutations is likely to increase, making genetic analysis crucial to understand the diseases (Lupski et al 2012). The ontology of the spectrum of different diseases will be based on the molecular profiles of genes and mutations that will be identified and characterized in every subject and disease. This ontology will integrate the complexity of the mutational spectrum of the genome with a simplification on the genes that carry the crucial combination of genetic variants for each phenotype.

2.4 Longitudinal genomics data and integration with biological and clinical data

As soon as accurate sequencing of human genomes becomes cheap(er), it is expected that an individual will be able to have copies of their sequenced DNA in their own computing devices, using it for medical, identification and social purposes. At the level of genotyping data, with over one million DNA variants generated, commercial laboratories [23andme (www.23andme.com), Navigenics (www.navigenics.com), and GenePlanet (www.geneplanet.com), among others], have provided genetic tests for *ancestry information and health questions*. It is highly likely that once DNA sequencing technology is sufficiently robust and cheap (at the technology and bioinformatics levels), all subjects will have their genomes sequenced at different time-points through life.

There are *many layers of genomics data* that can be produced from an individual (often referred as 'omics'). Omics data include many different types of biological information of a given subject -

relatives in a family can clarify who is affected, a carrier, or unaffected. Genetics data is often complemented with linkage, molecular, metabolomic, proteomic, and comparative genomic hybridization and expression data. This is often the case of studies in cancer samples and in disorders of an unknown nature that need deep characterization of their biology and genetics.

Genomic information produced using omic approaches has a clear continuous value for the individual. Firstly, the biological information obtained from each subject has the imprint of the individuality of the genetic characteristics of each person. These genetic characteristics translate into specific knowledge on biological questions on ancestry and health of the individual. Due to the continuous work in deciphering the components of human biology, physiology and pathology, the accumulating genomics information that is being produced at all levels is increasing new knowledge. This gives an enormous value to the information stored from each subject for further characterization as new information on the genome is produced and deciphered. Secondly, the collection of individuals' biological information has a value for other individuals when assessing specific aspects of ancestry, health and disease. Thus, the *individual value of genomic data* combines the data of each subject with the information generated from many other subjects. This added value at the level of the community has enormous implications for the individual understanding of the genome variability and its relationship with health and disease for everyone.

It is now clear that genomics data will be obtained at many time-points along the life of each individual. On the basis of different life events, the transcriptome, metabolome and other –omic profiles will be obtained and analysed several times and will be evaluated as new biological knowledge is produced and integrated. *The integration of clinical information with genomics data* is an essential step in the process of making personalised medicine a reality, directing the identification of genomic information towards: a) predicting the susceptibility to given diseases; b) evaluating the course of a disease; and c) predicting response to treatment.

The collection of genomics data at *many time-points* and the continuous evaluation of different types of data present many challenges. These include storage capacity, computational power, security, efficiency and cost. There are several initiatives to discuss all these aspects and the need for a global sharing of genomic and clinical data has been debated.

2.5 Security, privacy and accessibility of genomics data

From the population health perspective, producing and sharing as much genomic information about individuals as possible is to be preferred. From the individual perspective however, this raises several concerns regarding the security, privacy and accessibility of this data. In order to address these questions, we should start by identifying a set of general *issues around the processing of data*, including data storage and access, preservation of privacy, and aspects arising from data misuse or loss (stigmatisation or discrimination). A second aspect is more philosophical, since it examines the basis for individual autonomy and consent - and the extent to which existing practices might change in response to –omics information of the individual. A third aspect involves the professional practice, especially the implications of additional or incidental findings in both research and clinical studies.

Some of the results of genetic analyses may not relate to the initial purpose of the study. Some of these results are described as additional or *'incidental findings'* (IF), and they fall into three categories: a) variants with unknown or no clinical significance; b) health-related variants with implications for the individual and/or their relatives, but with variability in the predictive value and clinical utility; and c) findings that have a personal or legal significance. An IF is a finding concerning an individual genome study that has potential health or reproductive importance and is discovered in the course of conducting a genetic test that has other purposes, beyond the aims of the study (Wolf

et al. 2012). IFs are on variables not directly under study and are not anticipated in the genomic studies protocol of the research or clinical study.

Geneticists, investigators, institutional review boards (IRB), patients that participate in genomic studies, and their families, face the important problem on how to deal with IF. If geneticists unexpectedly discover any information that could be of potential health or reproductive importance, it has to be seen if they should inform the patient about the finding and seek for further advise or information. To what extent could the finding be an opportunity for the patient to modify important aspects of his or her life on the basis of the discovery in the genome? What should consent forms and the entire consent process say about how IF will be handled in genomic studies? What do the IRB require to define opportunities on the incidental findings in genomic studies? Returning genetic IF to individuals requires that the investigators communicating the results have the appropriate genetic training and expertise. Genetic risk for complex diseases is very difficult to evaluate and might lead to the common practice of not returning genetic IF to individuals. It is important to understand what kind of research information participants may want, and to consider the scope and nature of the *responsibility to communicate results* from the aims of a study, as well as genetic IF that may affect a person's health. The issues of whether and how to return IF should be considered when determining which results from a research trial will be reported. Sharing individual results from a research project, including IF, should be discussed explicitly in the consent form.

It has been proposed that genetics or genomics data have characteristics that might deserve special protection. These include its predictive potential, its probable impact on the family of the tested individual, and the physical nature of the genetic material. Stringent levels of *confidentiality, privacy and data security* will be necessary for the storage of, and accessibility to, genomics data. While most health records are related to measures of health and disease status, genomics data contain a complete set of information on aspects that could be related to biological aspects of the individual that could affect current or future life, but that may not have immediate consequences for his or her health. Moreover, not all the information will be available at the time that the genomic studies are performed. Therefore, the clinical access to genomics data should be delineated in layers on the basis of the questions posed with respect to health. These layers will be related to the specific questions that we can plan to solve for specific medical purposes along the life of the individual.

One could thus foresee a *stepwise process for the release of generated genomics data*. In an initial study performed on a parents & child trio after birth, the data could be evaluated to elucidate potential metabolic or serious disorders that could affect the development of the child, but not exploring the rest of the genome at this point. Later along the life of the child, further studies could be performed to address specific questions that might be important from the point of view of exposure to infectious agents, surgery challenges, and response to pharmaceuticals. The genome could further be explored for genomic information that could be relevant for a serious clinical event that the child might have suffered. None of these studies would disclose any information that could be relevant for adult onset disorders for which we do not yet have tools for prevention and treatment.

There are several *purposes for storing genome data*: a) individual genomic data for diagnosis, prognosis and management of disease of the individual; and b) aggregated anonymised genomic data obtained from many individuals for the generation of information for genomics results in the future (of value for the community and the individual). The storage of genome information in a clinical context has many implications and raises several concerns. These include the storage capacity, the speed of the network for transferring data, the integration with electronic medical records (EMR), and the access for further analyses of data. Ethical issues related to the storage of data include consent, confidentiality, privacy, access, and possible misuse that could lead to stigmatisation or discrimination.

As the result of several research projects studying specific disorders together with individual data obtained in the clinical context or via direct-to-consumer testing companies, there is a large amount of genetic data that has been *generated and stored at many locations* (Bloss et al. 2011). Access to genomics data stored at (private) genomic companies is now a matter of concern due to the benefit of using this data for the community as a whole. This has caused controversy and led to specific actions to compile the data from customers and to make that data accessible to the scientific community.

2.6 Public genomics data – layers of public use and individual value of genomics data

Genomics technologies are likely to stimulate a more systematic *use of electronic medical records* (EMR). Paper-based records are extremely costly when compared to the duplication and transfer of digital records. However, the portability and accessibility of EMR may increase the ease with which they can be accessed and stolen by unauthorized persons. This can include discharge/transfer orders, pharmacy orders, radiology results, laboratory results and any other data or provider notes. Some EMR systems can perform automatic monitoring of clinical events to predict, detect and prevent adverse events of treatments. EMR can connect medical practitioners to researchers, facilitating clinical research. This mode of communication improves the quality of primary care and increases clinical research opportunities, facilitating the translation of research into primary care.

Genetics and genomics data will become part of the clinical record of an individual. However, the fact that the genomics information has many features that are not directly related to the current health of the patient but with the potential and predictive nature of the genetic characteristics of his or her biology, makes this information much more controversial than other clinical data. Genomics information must be kept confidential and secure and should only be accessible for specific purposes and by specifically trained staff.

As EMR becomes more systematised, questions may arise about the responsibilities of health professionals regarding *access to genomics data at relevant times* in order to optimise its use for the health of the patient and family (when reaching adulthood, or when planning to start a family, for example), or when new scientific knowledge arises that might be relevant to a current diagnosis or for future prevention. Although some of these issues apply to limited genomics data from an individual, the complexity and scale of genome sequencing data is much higher.

The complete size of a genomics stored data file has major implications for *data transfer for analysis, safe archiving and data interpretation*. A system will need sufficient capacity in order to transfer terabytes of data - far beyond the current capacities of public or private health system networks. While it should be feasible to use removable disks, this does not facilitate safe and controlled data sharing between individuals who might need different levels of access to some or all the data for various purposes. Cloud computing has been proposed as a common solution to distribute and process data across multiple large hardware clusters. The main current limitations are the network bandwidth, and the security and confidentiality issues. However, it seems clear that a combination of cloud computing with dedicated servers that provide complete security on storage and analysis of the data will be part of the solution to this problem.

It has been argued that *only the specific clinical data* should be stored, and that the rest should be discarded from the EMR of the individual. Several analysts have argued that once the price of sequencing is low enough, there will be no need to store the individual genome data, and only specific test results should be stored in the EMR, because it would be cheaper to simply sequence again the genome. However, at present, it seems irresponsible to discard –omics data that has been produced.

2.7 Conclusion

There are many ways in which it should be feasible to access only the information that is needed at any one time, without the need to delete other information which could be of use in future evaluations of an individual's health. Thus, it seems desirable to collect *different layers of information* that could be of value for a wider population or other individuals, and in order to evaluate specific questions that might affect each person at different time-points of their lives.

3 Genomic medicine: challenges for its implementation from bench to bedside

Milan Macek

3.1 Introduction

There are different visions of what the future of public health genomics will look like. Most of these visions refer either directly or indirectly to P4 medicine – medicine that becomes predictive, preventive, personalised, and participatory. This chapter takes P4 medicine as an example. It starts by explaining the concepts of genomic medicine (3.2) and P4 medicine (3.3), and then discusses some of the challenges and preconditions for the successful translation of Genome-based Information and Technologies (GBIT) from the research phase to the clinic. The discussion will result in identifying a range of pressing policy issues raised by P4 medicine (3.4, 3.5).

3.2 The concept of genomic medicine

The sequencing of the human genome (Venter et al 2001) has fostered a quantitative and qualitative transition both in the study of rare (so called 'Mendelian') and multifactorial diseases and led to the development of more targeted therapeutic models. These rapid developments have enabled the concept of *genomic medicine* (Scheuner, Sieverding, Shekelle 2008) where clinical care is related to the interpretation of individual genomic variation. This type of advanced practice is dependent on the ability to establish clear disease-genomic variant associations which require the availability *of either well characterised rare disease patients (or families) or sizeable epidemiological studies* in multifactorial conditions, both of which require *strong informatics platforms* (Ning and Montgomery 2010).

The implementation of genomic medicine in clinical practice depends on properly designed *prospective studies* with well-established clinical and not just 'surrogate' outcomes. Further attention should be paid to the scientific rigour of genomic medicine clinical trials and their long-term sustainability. It is also necessary to develop new clinical trial methodologies, including adaptive clinical trial designs (Nelson 2010) taking into account *evolving evidence* of the pathogenic potential of genomic variants.

Policy issue: Need for long-term, sustainable, genomic medicine clinical trials in association with bio-banking (see ESFRI project – www.bbmri.eu).

3.3 Genomics in the context of P4 medicine

We are currently witnessing a transition from so called *'reactive medicine' focused on disease management*, to a *personalized, predictive, preventive and participatory medicine* ('P4 Medicine') which aims at the preservation of health (Hood et al 2008). It needs to be stressed that P4 medicine is one of the proposed future concepts of medicine and there are alternative scenarios as elaborated further. Nevertheless, for scoping future scenarios of genomic medicine we use P4 medicine as an example.

The practice of medicine is now undergoing a principle change of its basic paradigm. Such transition is fostered by advances originating in the field of basic sciences, e.g. sequencing of the human genome, rapid developments in the area of high-throughput 'omics' techniques, unsurpassed growth in informatics tools linked by the internet, including advances in microelectronics (Moore´s law) and associated development of high resolution imaging techniques (e.g. computer tomography, nuclear magnetic resonance-based imaging). Application of these technologies has the potential to move

medical research from the current *biological reductionist principle* towards *networks and complex system-based approaches* (Loscalzo and Barabasi 2011)**,** thereby radically changing the provision of health care.

Medical reductionism

Current medical research and practice are based on the assumption that the *dissection of complex biological phenomena* into smaller 'research issues' makes them more easily amenable to our current technical possibilities and *to human reason/logic -based examinations*. Accordingly, medicine itself has been divided into specialties (e.g. endocrinology, neurology) as a part of such reductionist strategy, while most scientific breakthroughs now occur within interdisciplinary collaboration (e.g. 'neuroendocrinology' in close collaboration with 'neurogenetics'). Although this strategy has been very successful and *led to the current high level medicine*, it is reaching its inherent limits with regards to the study of multi-factorial diseases. The transition from health to disease in an individual patient involves multiple causes (often individually minute) and requires complex interplay of different structures (systems) in the development of a given disease state. Some authors propose that models involving complex modelling of airline accidents apply to multifactorial diseases, as well (Bunnik, Schermer, Janssens 2011). Therefore, patients and health professionals need to understand that the 'causal' role of genomic variants is often minute (rendering a relatively small relative risk of 'failure'), as multiple genome-wide association studies has confirmed and that disease status arises only after a very complex interplay of individual factors.

Moreover, current advances in personalized medicine are based on statistical extrapolations from genomic research performed in stratified population/ disease groups, rather than assessing the individual patients itself (Regierer et al 2013). With few exceptions, as shown in the case of rare diseases, it is becoming increasingly evident that *complex outcomes cannot be attributed to individual biological entities*, e.g. merely genomic variants (i.e. genomic biomarkers in the broader sense). Complex interactions between DNA, RNA, proteins, but also their cellular position and tissue specific function, complicate the matter enormously and cannot be addressed by reductionist approaches, yet alone by human reason and/or our sequential analytical capacity. Furthermore, it needs to be stressed that genomics are *only upstream in terms of their biological complexity*, with proteomics being even more complex, by at least several orders of magnitude[1]. Protein versus protein interactions are also highly complex (Stelzl et al 2005).

The same issue applies to the field of *epigenetics*[2] with the quantification of the role of environment and lifestyle being in its conceptual infancy (Sanderson, Wardle, Humphries 2008). Quantification of *transgenerational effects* is only starting to be considered (Nadeau 2009). Essentially, medical genomics will become part of the integrative *'Big Data' society'* (Murdoch, Detsky 2013) that will integrate all available information for the benefit (but potentially, also for the detriment) of the apparently healthy individual.

Personalised (stratified) versus personal medicine: the facilitating role of human phenotype ontology

The challenges faced by genomic medicine are unprecedented given the vast heterogeneity of issues to be integrated – volume of data, data formats, informatics platforms, software, molecules, disease models, various diseases themselves, relevant tissues, nomenclature, methods, institutions, stakeholders, clinical classification schemes etc. all in the absence of a common biomedical *lingua franca*. Thus, *personalised (stratified) medicine* still has to be transformed into *personal medicine*, utilising proven concepts of *personal genomics* (Zazzu et al 2012; Ashley et al 2010).

1 http://www.hupo.org/

2 http://www.epigenome.org/

An important bottleneck for the implementation of P4 medicine is represented by the traditional *Oslerian/Virchowian reductionist approach to disease phenotyping* represented by *clinico-pathological correlations* that were developed during the late 19th century (Osler, 1892). Essentially, subjective clinical observations are linked with ('snap shot') *end stage pathological findings*. Therefore, a given disease is defined on the basis of the principal organ involvement in which clinical features manifest, and to which imprecise pathology and histopathology disease aspects are correlated. Hence, *current disease classification of disease phenotypes is too general,* which thus substantially limits consideration of additional 'pathophenotypes' within the individual context of a patient. Some authors suggest that in addition to next generation genotyping, we should also develop *next generation phenotyping*.

Moreover, the traditional phenotyping approach *does not account for preclinical disease susceptibility and all other associated gradual processes that tilt 'the balance' from 'apparently healthy' status towards a given 'disease*'. In addition, diseases are delineated (diagnosed) from the 'apparently healthy status' mostly based on the *development of clinical symptoms* in a patient. Symptoms occur only at later stages of the disease process and their assessment is subjective (both by patients and doctors) and prone to substantial bias by individual clinicians, even within one specialism. In this context, some patients come earlier when having 'suspicions', while others only come with full-blown manifestations of a given disease. Very little has changed in clinical education and given the biological complexity, the practice of medicine is traditionally viewed as an 'art', rather than an exact biological discipline with the underlying genomic approaches.

In other words the current disease classification is *grossly outdated, and end stage single-organ based, thereby precluding full implementation of genomic medicine into clinical practice* (Cucurull-Sanchez L, Spink KG, Moschos SA 2012). These shortcomings account for limitations in major genome-based initiatives to define disease 'associations' (usually wrongly termed as 'determinants'). These include the weak effect size of linked variants in genome-wide association studies of complex disease (i.e. phenomenon of missing heritability) and substantial *attrition of the majority of promising drug candidates*. Thus, solving this core problem of the current medical approach is not simply an academic exercise, but is essential for moving the current medical research from bench to bedside.

First initiatives to conduct in this regard are in the area of genomic medicine, where the prerequisite is to provide a comprehensive disease to genome annotation using *Disease Ontology* approaches (Osborne et al 2009). These utilize Unified Medical Language Systems (van Mulligen 1999) and include concepts from outside the disease/disorder semantic network including various cancers, congenital abnormalities, deformities and mental disorders. While many researchers have mapped diseases to Medline MeSH terms[3] or OMIM (Amberger et al 2009) the Disease Ontology is broader and provides more precise disease coverage. The hierarchical structure of disease ontology also allows more general disease terms to be distinguished from subclasses, in order to account for 'over-mapping/under-mapping' of diseases to genome variants using current textual description of pathophenotypes employed in current clinical medicine. Computational approaches to the human 'phenome', utilizing *human phenotype ontology* together with their annotation to complex biological data, is very promising to transform genomic medicine and improve health in the future[4].

Based on recent modelling of genomics data, some authors propose an entirely new approach to disease classification based on how genomic variants interact within a hierarchical network in

3 http://www.pubmed.com

4 http://www.human-phenotype-ontology.org

association to a clinical condition: a) based on the primary molecular abnormality (genome or proteome); b) secondary molecular abnormality (modifier genes; secondary genome or proteome); c) variants and/or their haplotypes (intermediate phenotype) that influence each response to stress (inflammation, apoptosis, reparative processes); and d) environmental / lifestyle effects. Accordingly, targeted therapeutic interventions could be devised, including dosage optimization based on the genomic, metabolic profile, circadian rhythm etc (Nambiar, Gupta, Misra 2010). It is therefore necessary to perform well-designed studies aimed at re-classifying human disease at a molecular level, mainly on exactly defined patient cohorts, from various populations. The concept of *efficacy* of *newly developed therapies, and not just drug therapies, needs to be redefined according to genome variant-based substratification and not just according to subjective (symptom-based) clinical evidence* (Urbach and Moore 2011).

Before the vision of personalized (P4) medicine is to become reality, vast amounts of digitalized personal medical data must be collected, analyzed and *properly integrated* (Lehrach et al 2011), for which an automated exchange of data and highly developed information technology will be necessary. Furthermore, there are substantial informatics challenges (Corander et al 2012) related to grid-based network (super) computing. Novel informatics *dynamic algorithms* will need to be developed for the study of treatment-induced perturbations in biological networks *in silico* (Bertini, Luchinato, Tenori 2012), i.e. *computational clinical assays*. In this regard, it has to be stressed that currently *we are only at the very beginning*, with genomics studies only being the initial inroad into the entire complexity of biology of health and disease (Simmons et al, 2012).

Even experts in the field need to get acquainted with novel concepts, terminology and realize that genomics is not the only factor determining the complexity of life (Carlberg 2012). It is now becoming apparent that the success rate of genome sequencing is largely determined by the quality of clinical characterisation of families under study, requiring multidisciplinary interaction of many medical specialities. Last but not least the entire health care and pharmaceutical 'business model' will have to adapt to personalised approaches based on genomics (Hall and McCabe 2013).

Policy issue: more studies are necessary in order to move beyond the current state of the art in medicine, i.e. from evidence based personalised (stratified) medicine to personal (individual) medicine.

Clinicians are not prepared and insufficiently trained to utilise novel concepts in P4 medicine

Development of P4 medicine will require substantial education efforts focused on the general public and physicians, since both will have difficulties in understanding the complex biological aspects, and *probability based concepts* which come out of from systems biomedicine, including its legal and ethical implications. For the *majority of clinicians, P4 medicine is a distant and generally unknown concept*. The entire healthcare sector (pharmaceutical companies, healthcare providers, insurers etc.) will also have to transform in the years to come (Florence and Lee 2011). Multidisciplinary teams involving clinicians and scientists, including *clinical informaticians* (Liaw and Gray 2010), need to be introduced into health care in order to translate new developments in genomic medicine into medical practice.

Medical services need to ensure there is an understanding between the doctor and patient of *what will be tested, what will not be tested, and why*. Moreover, there is a necessity to develop approaches that protect confidentiality while maintaining the ability of genomics to predict risks for relatives as well as for index cases, i.e. patients. Clinicians will need to know when and how results from the index case ought to be communicated to their relatives, in the context of evolving interpretation of genomic variants as previously highlighted. Furthermore, doctors must bear in mind that some patients may choose not to undergo genetic testing at all.

Within the future 'holistic approach' to an individual patient, clinicians will not view *incidental (synonyms: unsolicited, unsought for, secondary, untested for) findings as 'problems', but rather opportunities for the individual patient and their family.* Genome sequencing studies provide evidence that each of us carries approximately 100 deleterious mutations, however, only a few of them will lead to a disease during one´s lifetime. This was demonstrated by the fact that James Watson bears a number of deleterious mutations in his 'public genome' from the current point of view of genetic diagnostics. Each of them would have been associated by prevailing reductionist, associative, principles with severe hereditary conditions unless viewed within the context of age together with all other clinical and/or laboratory findings[5]. Thus, the mere presence of a pathogenic alteration in the human genome, with few highly penetrant exceptions in the area of rare diseases (Palau 2012), does not automatically lead to 'phenotypically apparent' disease status, as there are more shades of grey which only now we begin to appreciate (Lyon 2012).

Policy issue: Clinicians need to be trained in basic concepts of personalised/personal medicine.

Pharmocogenomics and precision medicine

Pharmacogenomics needs to be 'resurrected' *by systems pharmacology* (Allerheiligen 2010) after previous failures based on *premature application of genome-wide association studies (GWAS) concepts* which generally failed to provide causative and/or stronger scale correlations within the last decade. There is increasing understanding that we cannot keep developing drugs that will work only in a minority of patients for which they are developed. Patient and physician education is crucial to provide more realistic scenarios and convince the entire healthcare system of the potential benefits of individualized treatments. It also needs to be stressed that business model for drug development should be rethought, utilizing lessons drawn from rare disease-related *orphan drug development strategies* (Tambuyzer 2010).

Essentially, there is a growing need to develop an integrated model that could reliably predict treatment approach in individual patients – i.e. the concept of targeted therapy or *'precision medicine'.* This need is augmented by the rapidly aging population of the developed world, where for the largest European economy it is estimated that by 2050 the number of persons aged over 65 years will increase by 38% and the number of individuals aged over 80 years will increase by 156% (Peters et al 2010).

Harnessing the benefits of genomics by mainstream medicine via education and honesty

One of the greatest challenges is to ensure that 'non-medical genetic' (mainstream) specialties harness the benefits of genomic technologies. This is particularly true for primary care physicians, who mostly (and unlike e.g. university hospital-based physicians) are not aware of the rapid advances in the field of genomics. In addition, a *sizable majority of physicians perceive genetic conditions as being rare, marginal and untreatable*.

Maximising genomic opportunities entails at the same time being aware of their *inherent limitations.* Unfortunately, some genomic projects in the past were 'oversold', while *media presentations* of current, and often fascinating research developments, indicate that genomic variants provide clear-cut answers to complex clinical problems, but which are not based on scientific evidence.

In summary, it is now becoming clear that *individual patient management* based on customized computer predictions of optimal and necessary therapies for single patients, via genomic medicine approaches, is the only way beyond the current state of the art.

[5] http://www.acmg.net

Policy issue: implementation of genomic medicine requires transparency and honesty from all stakeholders involved, that is properly balancing hope versus hype.

3.4 Patient consent and involvement in continuously evolving interpretation of genomic variation

Informed consent for the *multipurpose utilization* of biospecimens and annotated clinical metadata in genomic medicine, as *interpretation of associated genomic variants is evolving as evidence accrues*, has only been evolving within the last few years (Wendler 2006). Thus, the main qualitative difference between the current medicine (dealing with individual patients in the present time) and genomic medicine (dealing with the index case-patient and their genetic relatives in a continuous manner) is in the transition of a *'patient to a donor'*; one who consents to multiple use of their stored bodily parts (i.e. not only germline DNA) for the common benefit within current and/or future genomic research. In other words, accurate provision of genomic medicine is only possible when *individual clinical and genomic data are shared* and where individual genomic variant composition is *contextually interpreted* on the 'population and disease-specific background'. There is a need to *continuously interpret the genome sequence* during follow-up for an existing clinical problem or in a novel clinical situation (Khurana et al 2013).

Policy issue: patients need to be educated that clinical interpretation of genomic information evolves and that the process is continuous throughout their lifetime.

3.5 Consumer driven health care and empowerment of individuals: genomics meets informatics

Another important development, which is linked to the rapid advances in genomics and health informatics, is that *health care becomes increasingly consumer driven.* This development is changing the current *information asymmetry* between the physician and the patient (consumer). Patients are increasingly having the opportunity to utilise high quality internet-based medical information, access their electronic hospital (medical) records, to which sequencing data naturally belong. All of this could be performed at a distance and mostly from a handheld device (typically a smartphone). Internet-based information is not only empowering consumers (hence populations), but also, more importantly, *individuals themselves*. For example, genomic sequencing may indicate increased predisposition to certain drug interactions, enabling the patients to request a specific medicine. A combination of wireless sensors and genomic information will enable prediction and monitoring of e.g. diabetes and cardiovascular diseases, with the 'personalised informatics hub' being the smart phone (Evans, Dale, Fomous 2010).

Policy issue: more studies are needed on the consumer driven approach to genomic testing in the absence of clear, actionable, interpretation of genomic variants.

3.6 Clinical context remains the core principle with regards to the interpretation of raw genomic data

Despite all the fascinating technological developments there will be also *increased patient/consumer confusion (and concern) stemming from the unclear interpretation of genomic variants or probability-based risk figures* necessitating high professionalism, empathy and compassion during counselling on the physician´s side. Importantly, a clear *distinction has to be made between raw genomic data and its interpretation into medically relevant information*. Despite rapid progress, the necessary scientific and clinical evidence that would substantiate unambiguous clinical interpretation of genome wide sequence data is still insufficient. *Standardised databases of normal and pathogenic genomic variation* (at disease specific, population and Europe-wide level), together with analytical tools that

will enable harmonised clinical algorithms for medically-relevant interrogation of genomic sequence data are still fragmented and not harmonised.

GWAS (Genome-Wide Association Studies) have identified sections of the genome that increase/decrease susceptibility to common diseases by a small margin. However, the interaction of such risk factors or whether they operate in a multiplicative or additive manner, including their dependence on particular environmental variables, has not been satisfactorily elucidated. Moreover, GWAS data provide only *indirect association* with most common traits, necessitating subsequent distinction between primary- ('driver') and secondary ('marker') variation[6]. Finally, given the fact that *genomic analysis is generally only conducted once in a person's life*, false-positive and false-negative results may have severe consequences and need to be duly accounted for[7].

Thus, the role of the physician will be completely different in the near future: i.e. to *provide guidance, wisdom*, experience and critical appraisal of information compiled by patients themselves from the wealth of web-based clinical and genomic information. On the other hand *the role of the clinical (medical) geneticist will be to educate and guide other medical specialities in provision of such guidance within their own specialties and provide the family-oriented context*. Specialists are much better equipped at providing information on a specific disease, while geneticists provide either the trans-generational or family context of genomic findings, in a complementary manner. A patient may utilise genomic testing to guide their medical management, while their relatives may use the same information for their reproductive decision-making and to avoid the birth of an affected child (Green and Guyer 2011).

Another issue that particularly needs to be addressed in the context of genomic medicine is that *the prognostic impact of genetic data is sometimes overvalued* with regards to other important factors such as education, environment and experience. For instance, there could be cases when research results associating genetic factors with e.g. intellectual disability are unduly perceived as 'stigmatizing' by those concerned, given their specific social environment, e.g. in studies in minorities, different racial groups, less privileged ethnic groups such as the Romani population. Thus, out of proportion misperceptions should not lead to 'draconian' restriction on research and public health measures such as newborn screening, but rather be dealt with by honest and contextual provision of culturally specific information (Bailey et al 2008).

With the exceptions of unambiguous genotype-phenotype correlations in a limited group of rare, monogenic conditions, genomic associations for common multi-factorial disorders derived from population studies are not 'automatically' applicable to individual patients. GWAS data merely represent statistical associations and not 'causal' variation for individual patients. Similarly 'causality' of identified genomic variants needs to undergo deep scrutiny and has to be standardised across various studies.

Patient concern naturally exists irrespective of whether samples undergo biochemical or genomic analyses, the latter still being of particular concern. Genomic information derived from the germline DNA may not only be pertinent to individual patients but also *exposes their first degree relatives*, who *had not consented* to the analysis of their genome. In the research domain, study participants should nevertheless be able to consent to the analysis of their own samples without the need for additional relatives' consent. Consequently, genomic information gathered from patients should not be forced upon their relatives. This problem is augmented in the case of rare diseases where due to the small number of cases their *re-identification* could be achieved by a combination of unique

[6] http://gwas.nih.gov/

[7] http://www.eurogentest.org

genomic and/or clinical variables. Therefore, a vitally important concern is to assure that participants in genomic research and their relatives receive adequate protection as stipulated by the *Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes* (Lwoff 2009).

Policy issue: medical professionals and the lay public should be informed of the complexity of interpretation of genomic data; clinical (medical) geneticists should educate and guide other medical specialities.

3.7 Conclusions

The translation of genomic research outcomes into the clinical practice still faces substantial challenges. Realistic expectations should be put forward since there is a lot of hope for a better future. However, the scale of complexity that has to be tackled and integrated for the provision of personalized/personal medicine also requires a prudent strategy which avoids hype and offers realistic expectations. Education of professionals and lay public is insufficient and requires innovative concepts in order to have the broadest possible impact. Proper communication of all such developments to the public and policy makers will ensure trust and foster sustainable developments in economically difficult times.

4 Genomics in medicine: societal approach and challenges for its translation and application in public health care

Irma Nippert

4.1 Introduction

There is consensus in the international debate that the rapid advances of new genetic technologies that provide detailed sequence information such as next-generation-sequencing (NGS) and whole-genome-sequencing (WGS)

(i) will reduce dramatically both the cost and the time required for NGS and WGS and that this process

(ii) will impact the practice of medicine and population health and spawn novel challenges that will go beyond those posed by traditional genetic testing applications.

Applying genome-based technologies in medicine offers many potential benefits, however the challenges health care systems face to assure a safe and effective translation are daunting and need to be thoroughly considered. Below some of these challenges and potential difficulties will be addressed.

4.2 Lack of biomedical informatics infrastructure and expertise

All health care systems are faced with the problem of how to develop an adequate infrastructure for processing, storing, and maintaining genomic sequence data and in providing expert support for applying NGS technology and WGS in the clinical context.

A tsunami of genome data generated by NGS and WGS threatens to drown existing structures and overwhelm providers if the need for capacity building, system strengthening and resource allocation is neglected.

In addition, the storage of individual linked genomic data, with the potential of reanalysing it whenever deemed appropriate, has major ethical implications such as: informed consent, access, confidentiality, data protection, feedback of findings - especially incidental findings, that need to be addressed and may require new data protection legislation in some countries. The current climate of financial austerity in many countries greatly affects the scope of health services that can be sustained in the public domain; the economic implications and costs for meeting training needs and improving infrastructure need to be considered and accounted for. So far, no country has assessed/evaluated its current state of readiness to implement and apply NGS and WGS and the wider economic implications of the implementation.

4.3 Insufficient knowledge to interpret genome-wide sequence data and to guide the assessment of their clinical relevance

At present, a wide gap exists between the capability to generate ‘more data for less money’ and the ability to interpret and understand the clinical impact of genome sequences in the absence of valid knowledge about the clinical and/or phenotypic impact of the majority of genome variants. Without the availability of effective robust databases that allow 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 NGS and WGS in clinical practice, in the absence of clearly defined pathways, will inundate physicians and patients with meaningless and/or uninterpretable data.[8]

There are currently few standardized methods for data analysis in existence and a common genomic analysis platform is lacking. The PHG foundation has highlighted this problem in a recent report*: "Although there are shared approaches, neither a single unified reference data set nor a comprehensive integrated analysis exists […] different groups have tended to develop their own customized pipeline"* (*Next Steps in the Sequence*, PHG Foundation 2011).

The same holds true for numerous databases of human genome variations, their scope, content, referencing and nomenclature varies. This current development mirrors the state of genetic testing services in the European Member States in the late 1990s as documented by the Institute for Prospective Technological Studies' (IPTS) survey *Towards quality assurance and harmonisation of genetic testing services in the EU* (Ibaretta et al 2003). The survey, which included an inventory of genetic testing services in Europe, highlighted major problems and documented the highly variable quality of services, rules and procedures, the plethora of different practices, lack of standard operation procedures and quality assurance processes. These findings resulted in the recommendation to the European Commission (EC) to fund the development of a European network to interact to produce European harmonization of quality standards for genetic testing services. In 2004, the *Network for test development, harmonization, validation and standardization of services in human genetics* (EuroGentest) was the result.[9]

The same concerted effort may be needed today to fund international genome sequencing and application projects by the EC or other international bodies. International collaborations such as the Human Variome Project[10] or the Cancer Genome Consortium[11] have been established – however issues such as long term sustainability and management when seed funding runs out still need to be resolved.

4.4 Opportunistic unchecked market driven introduction of 'consumer genomics'

The pronounced 'more data for less money' appeal of NGS technologies and WGS is no doubt a crucial driver for their fast application, especially in the commercial, direct-to-consumer (DTC) sector.[12] As the retail cost for WGS continues to fall substantially, it is expected that in the future more companies[13] will offer WGS directly on the internet. This prospect has fuelled an international debate on how to protect unsuspecting consumers from harm. Unsubstantiated claims made by internet based DTC providers in the past exemplify the potential risk involved. To date, the still small DTC market is unregulated and in some countries completely unchecked. Major concerns concentrate on the lack of regulation and quality assurance standards that may compromise the responsible provision of accurate, valid results and their interpretation.

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8 'Enthusiasm-based' application of novel technologies is a common phenomenon in medical care especially in the application of genetic testing devices, aptly described first by Neil A. Holtzman in *Proceed with caution : predicting genetic risks in the recombinant DNA era*, Baltimore: John Hopkins University Press, 1989.

9 http://www.eurogentest.org

10 www.humanvariomeproject.org

11 www.icgc.org

12 DTC 'tests' are services that are sold directly without the supervision of a physician

13 To date, companies such as Knome (http://www.knome.com), 23 and Me (www.23andme.com), deCODEme (www.decodeme.com) offer individual genome sequencing.

The scant ability of asymptomatic, healthy consumers to critically assess offers and to fully understand test results and risk information may have detrimental effects on the 'worried well' who undergo testing and then overutilize existing health care facilities post-test (requesting further advise, follow-up tests and interventions). It remains to be seen how amenable to regulation this market and its global reach will be.

The future development and impact of consumer driven use of commercial personal genomic services is currently unclear depending on factors such as perceived utility and benefit of offered tests and the impact of future consumer protection legislation.

4.5 Non-genetic health care professionals' lack of genetic competences

In the short to medium term, NGS technologies and WGS will probably have the greatest clinical application potential as:

(i) a means ('replacement technology') to offer more accurate, flexible cost-effective genetic testing to improve the diagnosis of disorders with a strong hereditary component; and

(ii) for facilitating diagnosis, classification and management of individual patients (e.g. cancer patients).

However in all countries non-genetic 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. Therefore it can be expected that in the near and mid-term future, the prospect of effective translation of NGS and WGS 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 professional with expertise in genetics. The lack of genetic expertise is a persistent and long acknowledged problem and well documented by research (Challen et al 2005; Harris et al 2006; Calefato et al 2008; Plass et al 2009; Benjamin et al 2009; Nippert et al 2011). This lack leads to inequity of access to genetic services, and results in adverse effects for patients (and their families) including delayed referrals, delayed diagnosis (diagnostic odyssey), and delayed access to timely treatment and the best possible care options.

Non-genetic health professionals' use of genomic technologies without full understanding and sub-optimal/ indiscriminate use of testing options, may not only prove detrimental for patients but also expensive for health care services (*Genomics in Medicine*, PHG Foundation, 2012). Considering the limited resources in terms of both the availability of expertise and available funding, the scope of education and training needs of 'Genomic Medicine' – tailored to the specific work of each speciality and of primary care providers – needs to be carefully assessed and calls for innovative solutions.

4.6 Translating NGS technologies and WGS into health systems: stakeholder involvement

The issues surrounding the development, evaluation and implementation of NGS technologies and WGS into medical care and beyond are complex and will take place in an environment of limited resources, conflicting interests, competing priorities, high expectations, and against a backdrop of a wide range of concerns regarding the use and protection of genomic information and personal data. How these complexities can be dealt with not only depends on health care systems' varying resources and capacities for the integration of the new technologies, but also depends on the development of policy and procedural guidance for the use of NGS and WGS, and good practice development outlining health services' responsibilities and patient/families/consumer rights.
Guidelines and legislations already available for traditional genetic testing services can probably be applied when WGS replaces currently available genetic tests. However, guidance probably needs to be fine-tuned to the specific circumstances and purposes of NGS and WGS application such as:

- data and privacy protection of whole genome sequencing data
- the potential availability of extra information/findings gained from WGS
- assurance of robust informed consent and the right not to know including incidental findings
- patients' rights to access their data for subsequent uses for family members or other clinical diagnostic purposes (what constitutes limits on access to and use of genomic data generated in research, clinical care and consumer-initiated)
- the circumstances under which genomic screening should be offered (opportunistic screening versus proactively directed screening at a symptomatic population or population subgroups)
- development of models for data sharing by individuals

The development of such guidance and policies should involve relevant stakeholders such as a wide range of health professionals, patient and parent groups, health policy makers and other groups concerned with issues raised by WGS.

An essential component for the progress of WGS application is *"the need to share, compare and pool data"* (Presidential Commission, 2012). To date many individuals/patients have participated/are currently participating in genome sequencing projects worldwide. Researchers and physicians have a special collective obligation and responsibility to ensure this public trust. Civil societies have to sustain a balance that fosters the progress of science, medicine and health care for the public good and that protects its members from harm. Therefore it is essential to engage in policy discussion and in collaborative decision-making processes that engage relevant stakeholders including patient advocating groups and civil groups concerned with issues raised by WGS.

4.7 In conclusion: policy implications

As can be seen from the previous sections, bringing broad genomic data into both clinical care of individual patients and into public health services (services targeted at those identified at higher risk of disease) will change the provision of medicine and will require informed policies and strategies to secure a beneficial implementation and translation process from bench to bedside. The numerous novel implications that come along with the new genome-based technologies require democratic societies to develop a set of strategic responses on how to translate genomic advances adequately and how to best avoid dysfunctional, potentially harmful translation and misallocation of resources. Inevitably effective genomic medicine will be based on accessible genomic databases. Finding a balanced approach that respects and protects autonomous decision-making, confidentiality and privacy and accords 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.
Below are some of the issues policy makers need to address that are relevant to the translation process of genomic-based medicine into health care in civic societies.

- Ensure a *systematic (country specific) needs assessment for capacity building*, health care systems strengthening and the wider economic implications *in order to help health policy makers, health care providers and other relevant stakeholders to make informed decisions* for the application of new genomics based technologies in health care and to allocate adequate resources.
- Address the *challenge of non-genetic health care professionals' lack of genetic/genomic competences and promote public genetics/genomics literacy*. This includes the engagement and participation of (lay) communities and community advocacy organizations (i.e. patient organizations) to address their knowledge needs.

- Address the *challenge of unchecked market driven introduction of 'consumer genomics'* and major concerns regarding the lack of regulation and quality assurance standards to protect consumers.
- Support concerted efforts to monitor the current development of databases of human genome variations and international networks of data bases. Support a European harmonization process for the development of *shared standards and nomenclature*. Foster 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.*
- In order to harness the benefits of new genomics knowledge and to assure a safe and effective translation into health care it is essential *to engage civil societies in policy discussions in unbiased settings* and to ensure the participation of all relevant stakeholders (including patient advocacy groups and civil groups concerned with issues raised by the application of new genetic technologies).

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Part II

Issues of quality assessment and implementation

Report of Expert Working Group 2

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1 Established frameworks for the quality assessment of genomic tests

A. Cecile J.W. Janssens

1.1 Introduction

The assessment of genomic tests comprises the evaluation of a variety of aspects, including technical details, the predictive ability, the benefits and potential adverse effects of testing, and the organizational aspects and costs of large-scale implementation. Several professional organizations and government-sponsored initiatives have developed guidelines for the evaluation of medical tests. These guidelines emphasize that the evaluation of tests should take into account the specifics of the health care settings, populations and purposes for which a test is going to be used. The guidelines agree regarding the criteria that are considered of key importance: a (genomic) test needs to measure what it intends to measure, should predict an outcome of interest to a certain degree, and lead to improved health outcomes. These three criteria are generally referred to as analytic validity, clinical validity and clinical utility.

In building the evidence for the implementation of new applications in health care, two considerations are important. First, in contrast to analytical validity, the clinical validity and clinical utility differ between populations and health care settings in which the test is used. Therefore, also in the evaluation of genomic testing, the essential question to be addressed first is: what disease do we want to predict in whom and for what reason? The answer to this question determines in which population the clinical validity and utility should be assessed. Second, the evaluation guidelines also distinguish between levels of evidence. These range from single observations to randomized controlled trials to meta-analysis of multiple, independent studies. Higher levels of evidence, which could be meta-analysis for clinical validity and one or more randomized controlled trials for clinical utility, are required to justify the introduction of genomic testing in health care.

Building the necessary evidence for genomic tests thus asks, per application, for investment in multiple well-designed studies in populations that are representative of the population in which the health care application is foreseen. This is in contrast to the current interest in large-scale bio-banks, which are useful for epidemiological research, but not for the assessment of novel health care applications of genomic testing.

1.2 Evaluation frameworks for genomic testing

The assessment of genomic tests comprises the evaluation of a variety of aspects, including technical details, the predictive ability, the benefits and potential adverse effects of testing, and the organizational aspects and costs of large-scale implementation. Several professional organizations and government-sponsored initiatives have developed guidelines for the evaluation of medical tests, which address all aspects that are considered important for the implementation of the test in health care.[14] These guidelines were designed for different purposes and for different audiences, and therefore differ in the details. Yet, comparison of the guidelines shows that they each were not developed independently from scratch, but built upon each other and modified to fulfil specific needs of the target audiences. For example, the criteria of EuroGenTest, EGAPP (see box) and several national guidelines are based on the ACCE model but have been adapted to predominantly target clinical genetic practice (EuroGenTest) or to be broadly applicable to genetic testing in both clinical and public health practice (EGAPP). Not surprisingly, there is substantial agreement between the guidelines regarding the criteria that are considered of key importance: a (genetic) test needs to

[14] http://www.cadth.ca/media/pdf/EvalFrameworksGeneticTesting-es-37_e.pdf.

measure what it intends to measure, predict an outcome of interest to a certain degree, and lead to improved health outcomes. These three 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 ACCE model. These criteria will be discussed in this chapter.

1.3 Analytic validity

Analytic validity addresses the extent to which the test measures what it intends to measure (the measurand). In genetic testing, the measurand refers to genotypic information, which comes in many different types, from variation in the smallest DNA fraction (single nucleotide polymorphisms) to complete chromosomes to variations in the structure of the DNA. The definitions of analytic validity used by the various guidelines largely overlap. The ACCE model defines analytical validity as how accurately and reliably the test measures the genotype of interest, and USPSTF, which mainly addresses non-genetic health care applications, defines analytical as the ability of a laboratory test to accurately and reliably measure the properties or characteristics it is intended to measure.

Analytic validity is generally assessed as the test's ability to correctly detect the presence of the genotype (analytic sensitivity) and the absence of the genotype (analytic specificity), but quality criteria may also include the repeatability of the test results, for example, which is the agreement of the test results for independent assessments of the measurand. The latter is particularly important for new technologies.

Figure 1.1. Key Guidelines and Resources for the Assessment of Genomic Testing

Fryback-Thornbury Evaluation Framework *A hierarchical 6 level model, originally developed* for the evaluation of the efficacy of diagnostic imaging tests (Fryback & Thornbury, 1991).	
ACCE	A model for the assessment of genetic testing that comprises 44 questions to assess Analytic validity, Clinical validity, Clinical utility, and Ethical, legal and social implications (Haddow et al 2003).
EGAPP	Evaluation of Genomic Applications for Prevention and Practice, an initiative sponsored by the Office of Public Health Genomics of the Centers for Disease Control and Prevention (CDC): 'to establish and evaluate a systematic, evidence-based process for assessing genetic tests and other applications of genomic technology in transition from research to clinical and public health practice'. Based on the ACCE model.
EuroGenTest	A European initiative that encourages the harmonization of standards and practice of genetic testing in the EU and beyond, and commissions the establishment and update of Clinical Utility gene cards. Based on the ACCE model.
USPSTF	The analytic framework of the United States Preventive Services Task Force: 'the leading independent panel of private-sector experts in prevention and primary care'. USPSTF is sponsored by the Agency for Healthcare Research & Quality (AHRQ), part of the US Department of Health & Human Services, which aims 'to improve the quality, safety, efficiency, and effectiveness of health care for all Americans'.
EUnetHTA	European Network for Health Technology Assessment: 'a network of government appointed organizations' established 'to help developing reliable, timely, transparent and transferable information to contribute to health technology assessments in European countries'.

Resources

Clinical Utility Gene Cards Structured reviews focusing on the clinical validity of genetic tests, predominantly for Mendelian disorders, and their usefulness in diagnostic, predictive and prenatal settings, published by EuroGenTest.

GeneTests GeneTests, sponsored by the National Center for Biotechnology Information (NCBI), aims to promote the appropriate use of genetic services in patient care and personal decision making by providing current, authoritative information on genetic testing and its use in diagnosis, management, and genetic counselling.

NIH-GTR A public database of genetic test information, linked to GeneTests and GeneReviews.

1.4 Clinical validity

Clinical validity refers to the ability of the test to detect or predict the outcome of interest (ACCE) or the presence of absence of a clinical condition or predisposition (AHRQ) (Sun et al 2011). The outcome of interest is generally the development of disease, but it can also be severe prognosis of disease or death, or, pharmacogenetic testing, treatment response or the occurrence of adverse side effects of drug treatment. While the outcome of interest may vary between the tests that are assessed by the various guidelines, the definitions of clinical validity largely overlap.

Clinical validity is predominantly determined by the strength of association between the DNA variation and the occurrence of disease. This association is extremely strong in monogenic diseases, such as Huntington's disease and cystic fibrosis, but very weak in multifactorial diseases as type 2 diabetes and asthma, in which many other genetic and non-genetic risk factors impact the development of disease as well.

Clinical validity is usually assessed in terms of the test's ability to correctly detect or predict the presence of the disease (clinical sensitivity) and the absence of the disease (clinical specificity) and by related measures such as the positive and negative predictive values, which represent the risk of disease when the genetic variant is present and the 'risk' of not developing disease when the variant is absent. These different metrics are logically related, they can be calculated from one another, but they represent different information. Sensitivity and specificity indicate what percentage of the patients and 'non-patients' are correctly identified by the test, which is considered a population perspective. They do not indicate for specific individuals whether the test result will be correct. The latter is indicated by the positive and negative predictive values, which are more important from the perspective of the tested individual. A complete assessment of the test includes these various perspectives.

1.5 Clinical utility

Where clinical validity assesses whether the test is a worthy test, clinical utility refers to whether it is worth testing. A test that is very predictive is not always worth performing. An example is the genetic predisposition test for Huntington's disease, which is very predictive (has high clinical validity): all individuals who have the mutation in the Huntington gene will develop the disease and those who have not will not develop the disease. Yet, the test is only clinically useful for individuals with a family history for the disease and not in the general population. When parents and grandparents did not have the disease, the probability of carrying the mutation and developing the disease is absolutely zero. In other words, the test will certainly tell that the individual does not develop the disease.

What exactly is the utility of testing and what considerations are used varies substantially between health care scenarios, and hence the definitions of clinical utility between the available guidelines

show more variation. The ACCE model defines clinical utility as how likely the test is to significantly improve patient outcomes, and according to AHRQ it is the usefulness of the test and the value of the information to medical practice (Sun et al 2011): "Clinical utility represents a balance between health-related benefits and the harms that can ensue from using the information provided by a test. Those benefits and harms may need to be considered at the individual, family, and societal levels."[15]

1.6 Disorder and setting

In contrast to analytic validity, clinical validity and clinical utility are strongly determined by the context and setting in which the test is used. As illustrated above, the clinical validity of a test (predictive ability) depends on factors such as the population in which the test is applied and the length of the risk period. Numerically, and by definition, the two-year risk of breast cancer in 50-year old women is lower than the 10-year risk. And the 10-year risk of breast cancer differs between 30-year-old, 50-year-old and 70-year-old women. And the 10-year risk differs between women from the general population and women with a family history of breast cancer. Therefore, the essential question to be addressed first is: what disease do we want to predict in whom and for what reason? The ACCE framework explicitly addresses this as the specification of disorder and setting in the centre of the ACCE wheel. The answer is a qualitative assessment, related to the utility (for what reason?), which precedes the empirical quantification of the sensitivity and specificity. For example, when the aim is to assess the value of genetic testing for optimizing mammography screening, the two-year risk of breast cancer is more relevant than the 10-year risk when women are screened every two years. Yet, when the aim is to assess genetic testing in recommendations for prophylactic mastectomy, the lifetime risk is more relevant than the two-year risk (because women who do not develop breast cancer within two years, may develop the disease later). Note that to quantify the clinical validity of the two-year risk, only a study with a two-year follow up is needed, whereas the assessment of the lifetime risk requires a long follow-up.

The notion that the clinical validity and clinical utility differ between populations and health care settings highlights the importance of investigating the assessment of genomic tests in clinically relevant study populations. The current trend in health sciences is to establish large-scale bio-banks in which numerous research questions can be addressed. Particularly when the goal is to translate the research findings to health care practice, smaller studies in populations that resemble the target population of testing are ultimately needed to provide the required evidence.

1.7 Assessment of analytic validity, clinical validity and clinical utility

Assessment of analytic validity, clinical validity and clinical utility requires empirical research. Different types of studies are needed to provide the chain of evidence required for introducing a test in health care.

Analytic validity is assessed by comparing the performance of the test against a 'gold standard' - a test that accurately assesses the measurand with 100% certainty. This gold standard is often more expensive, inefficient, time-consuming or complex in other ways, which drives the need to search for new alternatives with more desirable features.

The assessment of clinical validity depends on the intended use of the test. In general, the most important distinction is whether the test is going to be used for the detection of the disease, such as in diagnostic and screening scenarios, or for the prediction of future disease. The clinical validity for the detection of disease is assessed in cross-sectional studies, which use a study design where the test and clinical diagnosis are assessed at the same time. However the clinical validity for the

[15] Sun (2011) citing SACGHS (Secretary's Advisory Committee on Genetics, Health and Society).

prediction of outcomes requires a study in which a population is followed over time to monitor who develops the disease. The selection of the study population and the duration of the follow-up, among other factors, are crucial in the assessment of the clinical validity, particularly when the risk of disease varies with age or between populations. A 30-year follow-up study in young adults or a one-year follow-up in the elderly will not be appropriate to demonstrate clinical validity for a genetic test for dementia. As indicated above, smaller studies in relevant populations are more useful for providing the required evidence than large-scale bio-banks in populations that are too young or too old, or otherwise not representative of the target population in which the genetic testing is ultimately foreseen.

The clinical utility of testing is assessed in various ways, and largely depends on the health care scenario and what is considered clinical utility in the specific scenario. Clinical utility can be considered present when the genetic test affects treatment decisions, or has psychological benefits, such as reduction of anxiety and the knowledge of knowing. It is also present in screening and prevention, for example, when the disease can be prevented or detected early in more individuals. The assessment of clinical utility generally goes beyond the impact on medical decisions, because a different treatment of screening strategy may not be a better one. Therefore the focus in the definition of ACCE is on the improvement of patient outcomes, rather on the information to medical practice as in the first part of the definition of AHRQ.

As well as the types of studies that need to be conducted, the frameworks also define the level of evidence that is needed. In general, one study is considered no study, and multiple independent studies are needed to confirm the clinical validity and utility of testing. EUnetHTA specifies that the evidence is preferably obtained from systematic reviews of (randomized) controlled trials, or if not available, from single controlled trials. If these are not available, non-controlled studies and respective systematic reviews can be considered. Note that when the evidence needs to come from multiple independent studies, investments in smaller studies are preferred. For clinical utility, health care register data or modelling studies can be conducted. These stringent criteria for the required evidence set high standards for the potential introduction of new genetic tests in health care and for research infrastructures (and funding) needed for tailor made quality assessment of new genetic and genomic tests.

1.8 Novel developments

The most promising development in health care will undoubtedly be the introduction of whole genome sequencing (WGS). Applications of WGS are foreseen in new-born screening, pre-implantation genetic testing, carrier testing, and are expected in commercial DNA testing. How do these developments relate to the definitions of analytic validity, clinical validity and clinical utility?

A major change compared with traditional genetic testing, in which specific DNA variations are tested to detect the presence or absence of disease or predisposition, is that WGS can inform about multiple health outcomes at the same time and that the results of one single test can be used later in various settings for various purposes. This will require a redefinition of what is considered ‘the test’ and will split the assessment in two parts.

WGS changes the definition of the test, because it will become even more important to distinguish the technical part from the information part (Zimmern & Kroese, 2007). In classical genetic testing, a specific DNA variation is tested to detect the presence or predisposition to a specific disease, with no explicit need to distinguish between a technical and information part. In WGS, the technical part refers to the sequencing as such, and the information part is what can be learnt from the sequence and what can be done with that information. The technical quality of the test is independent of the

setting and purpose of testing, but the informative value clearly is not. This has implications for the assessment of WGS.

The analytic validity, which is how accurate the whole genome can be decoded into data, is determined by the technology used, by protocols, by the quality of the laboratory and its personnel, and is (assumed) to be the same for the entire genome. In contrast, clinical validity and clinical utility are totally determined by the setting and purpose of testing and hence need to be determined for each application of the sequence data separately. WGS needs one assessment of the analytic validity, but numerous assessments of the clinical validity and clinical utility, from different studies with different study populations. Note that this does not change the definitions and assessments of analytic validity or clinical validity and utility as such; these will remain the same. It also does not change according to whether the disease is monogenic or multifactorial of origin. The metric used to assess the clinical validity does differ between the two, but their interpretation is similar. Sensitivity and specificity are calculated to assess the predictive value of the absence or presence of a mutation, whereas the area under the receiver-operating characteristic curve is calculated for genetic risk models that predict the risk of multifactorial diseases.

1.9 Conclusion

To facilitate a responsible translation of genomic research to applications in public health and clinical care, the following steps are desirable:

- In order to help build the necessary evidence for the assessment of genomic tests, we need to invest in well-designed studies in populations that are representative for the future health care application of the genetic tests. Because the setting and population are key determinants of clinical validity and utility, the studies need to be tailored; they do not need to be large-scale or to be multiple studies of the same design and methods. For the accumulation of evidence, multiple smaller studies in the intended population have more value than one analysis using data from a large, generalized bio-bank.
- Investments in education are needed to help policy makers, doctors and the population understand the opportunities and limitations of genomic testing. In the short term, education of health care professionals is most urgent. WGS will become mainstream in medical practice and once the sequencing is performed, doctors might find it tempting to use the information when it is available. Understanding when testing is informative and useful, making distinctions between prevention and clinical care, is vital.

2 Quality assessment of new genomic tests in the context of established practices of testing and screening

Inge Liebaers

2.1 Introduction

In this chapter we will discuss the introduction of new genetic tests in different health care settings, emphasizing the difference between 'classical' genetic tests and 'new' genomic tests. In Section 2.2 we take the standard framework for the evaluation of new genetic tests as a starting point for a description of different levels of assessment and validation of a laboratory test. We emphasize the importance of performing tests in an accredited laboratory, and taking part in external quality assessment programmes. These are mandatory conditions in order to deliver test reports of high quality. When introducing 'new' tests into health care, the existing frameworks for quality assessment should thus be used. However, there is a major difference between the 'classical' genetic tests and the 'new' genomic tests in that besides finding an answer to the question asked (diagnosing or predicting a medical condition), unsolicited information about unknown (up to now) abnormalities or serious health risks may become available. The question is, what should be done with this information. Solutions to overcome these problems are briefly mentioned. We then describe in Section 2.3 the state of the art by discussing examples of new genomic tests already used in the clinic or brought to the market. Finally, in Section 2.4, we describe the situation for tests that are likely (or unlikely) to be introduced in medical care in the near future. The conclusion is that before providing a new test, enough research data have to be collected about the validity and utility of the test, including coverage of ethical, legal and social issues. Moreover, a system to allow correct translation of a new test to public health care should be put into place, including necessary regulation.

2.2 Application of existing frameworks

The new genomic developments include new genomic tests such as microarrays and whole exome or even genome sequencing for health purposes. These techniques allow for analysing the blueprint of our genetic code with more or fewer details. They may be used for diagnostic purposes with potential relevance for therapeutic interventions. These tests provide a large amount of information about an individual's genome. *Genetic testing* is requested and performed in the context of addressing a personal or familial medical problem. *Genetic screening* is performed and offered by the provider in the context of tackling or searching for a possible risk or problem in a healthy population (Sequeiros 2012).

To implement a genetic test into health care, that is, in a clinical setting, many levels of assessment and validation are involved as described earlier (in Chapter 1 of the EWG 2 report). Professionals and clinicians have to decide whether a test has, or may have, clinical validity and utility in a particular health care setting. Other professionals involved in test development should decide about the analytical validity of a test by performing the validation (new test) or verification (existing test) of a specific test according to a standardized framework (Mattocks et al 2010). The laboratories where these tests are performed need to be accredited. An accredited laboratory needs a quality management system taking care of on-going test validation, document control, external quality assessment, internal quality control, internal auditing, writing a management review and people management (Berwouts 2010). Other important aspects of the quality management system are the correct labelling of the samples and the correct reporting of the results (Ravine and Suthers 2012; Berwouts 2012). A recent study showed that the quality of genetic testing varies widely in European laboratories (Berwouts 2011).

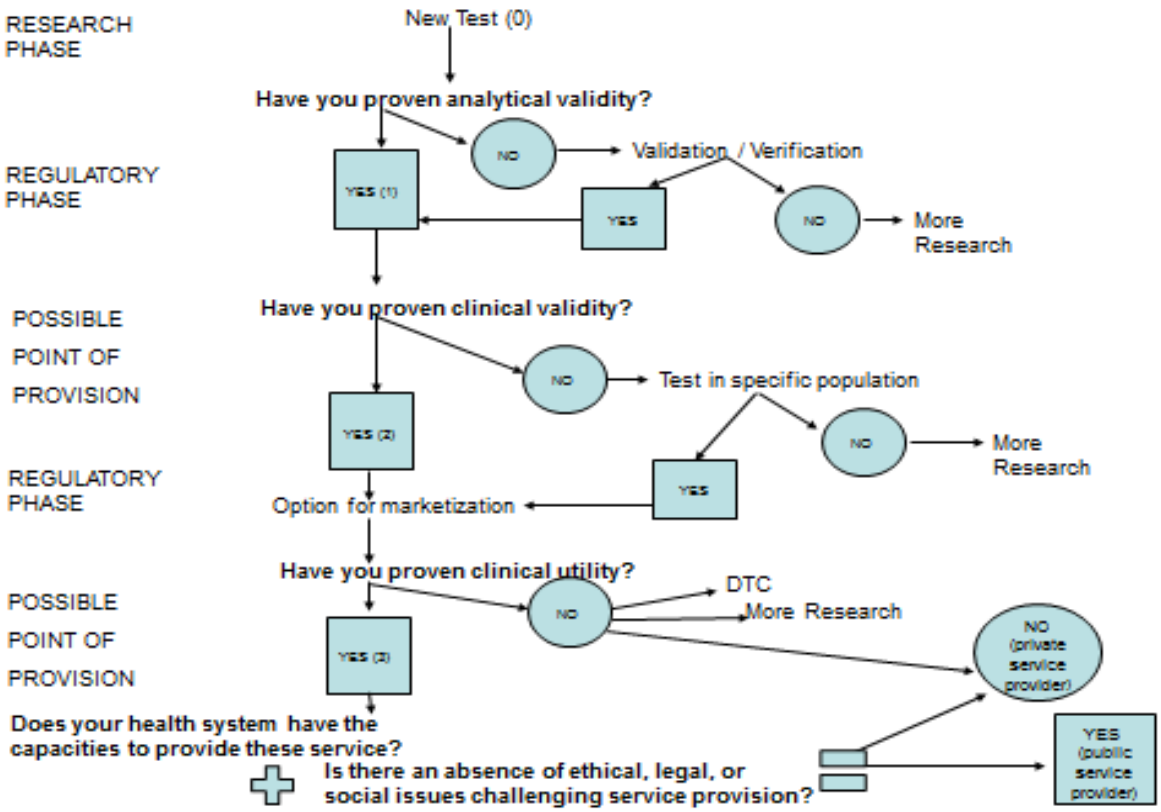
For monogenic diseases of which there are many - but all of them rare - diagnostic molecular tests have been developed over time for each disease separately. For some of these diseases only one or two mutations in one gene were found to be responsible. For others an endless number of mutations in one gene were found to be responsible. For still others several mutations in different genes were and are being described. For many of these diseases a large amount of information on analytical validity and clinical validity and utility is available on the diagnostic tests via the clinical utility gene cards (Eurogentest), gene reviews (NIH) and UK-GTN gene dossiers (NHS-UK) (Dierking et al 2013). Nevertheless, the cause, being a mutation in a responsible gene, has still to be found for many of these monogenic conditions. Moreover the contribution of our genome to the development of complex diseases, which occur much more frequently than the monogenic conditions, and to pathologies such as congenital malformations, with or without developmental delay, is being elucidated.

New genome-wide test methods as described earlier have been and are being developed in order to try to find the cause of the conditions mentioned above by analysing the complete genome at once instead of looking at bits and pieces consecutively. These new tests raise new challenges for the health care services and in particular, clinical and laboratory health care practitioners and providers, as well as for individual users and decision-makers in society. Also, more and more companies are interested in developing and offering tests to the different actors in the field. It is clear that these new tests may be very efficient and useful when appropriately used. Their potential is still increasing; the technology is improving and becoming cheaper. These new tests are challenging as far as quality assessment is concerned because (1) no golden standard exists and (2) large trials are impossible because many genetic conditions are rare. Therefore clinical and laboratory expertise must build evidence (Mattocks 2010; Hastings 2012). Nevertheless, the analytical validity, the clinical validity and utility of these tests have to be proven before their wide application.

Even more challenging is the fact that these new tests provide too much information, which at the moment is difficult to handle. This has started an on-going discussion at the societal, ethical and legal level and concerns the way in which these tests should be used or applied in the clinic and in the public domain (Hastings et al 2012). A major concern is that these new tests, by finding a novel mutation in a new gene or by finding a duplicated or deleted part of our genome, may find other abnormalities. Some may correspond to a known abnormality like a mutation in a breast cancer gene but also to an abnormality which has never been seen before which may not yet be related to a known disease or may be the cause of a yet unknown disease. The question here is, what we are to do with this unsolicited information? On the one hand, technical solutions to overcome some of the problems are being developed such as using targeted genome tests to limit the amount of data and information generated. On the other hand, ways of handling the problems are being developed by providing informed consent documents to the tested individuals, explaining the unsolicited or unknown information that might become available and asking them what they want to be told (Hastings et al 2012).

In the following sections new genomic tests will be discussed that are currently being introduced in a variety of established health care settings or that might be introduced in these settings in the near future. We will discuss the (potential) significance of these tests for finding answers to questions arising in the clinic and we will evaluate the available evidence for the quality of these tests. The following flow chart illustrates how to proceed with new tests in the process of translation from ‘bench to bed’.

Figure 2.1 – Public Health Genomics Tests: From Bench to Bed



This figure is a simplified schematic representation of how a new test may evolve from a research setting (bench) into health care (bed). The process is most of the time not as linear and far more complex because the analytical validity of a test and even more so its clinical validity and utility may vary according to the specific health care setting.

2.3 Examples of tests currently being introduced in (clinical) practice

New genomic tests are currently being introduced for diagnostic purposes and are proving their value mostly in postnatal and prenatal clinical health care settings.

Microarrays for postnatal diagnosis in children born with multiple congenital anomalies (MCA) and or mental dysfunction

When a child with multiple congenital anomalies is born or presents with mental dysfunction, the parents ask questions in the first place. Questions like why did it happen, how did it happen, what about the future, what are the therapeutic possibilities? And later on, questions like is there a recurrence risk in a subsequent child and if yes, is there a way to prevent recurrence? Health care providers should be able to answer these questions as accurately as possible. To be able to do this one has to find the cause of the problems in the first place. The use of microarrays is now more and more accepted as a first test in the case of multiple congenital anomalies (MCA) and/or intellectual disability, autism, or abnormal growth. Microarrays allow for the detection of an abnormal chromosome count (more or less than 46) or missing or additional parts of chromosomes (deletions or duplications) not visible before. Until recently the conventional karyotype supplemented with specific fluorescent in situ hybridization (FISH) test was 'the golden standard' identifying a number of chromosomal anomalies as the cause of unidentified MCA or related conditions. For this patient group microarray testing has become the first test to do because the diagnostic yield is higher and the approach has proven to be cost-effective (Miller 2010; Tradikis and Shevell 2012).

Microarray testing is analytically valid because the test not only identifies the same anomalies as the earlier 'golden standard' but many more, namely 20% versus 3%. The test is clinically valid to a certain extent because an anomaly is often (but not always) found. The test has clinical utility because the result allows action like genetic counselling, appropriate care, and may provide opportunities for further research. Quality criteria and platforms for use in the clinic have been published. They describe how to choose the platform, how to validate the test, how to write a report of the results based on the types of copy number variants (CNV). Those detected should be reported in terms of: (1) pathogenic and clinically relevant (the missing piece of the chromosome or micro deletion explains the MCA); (2) clinically significant but unrelated to the phenotype (the missing piece is known to cause a syndrome characterized by MCA but is different from the malformations presented by the patient who was tested); (3) variant of uncertain (clinical) significance (VOUS: a deletion or duplication is seen but cannot be linked to the malformations present in the patient nor to any known syndrome based on what is known today); (4) likely benign polymorphic CNV (abnormality which is quite common in the population and is of no relevance) (Vermeesch 2012). When correctly applied, as described above, this testing approach has passed quality control as depicted in the flow chart (figure 2.1) because analytical validity as well as clinical validity and utility have been proven.

Microarrays for high-risk prenatal diagnosis in case of ultrasound abnormalities or low risk prenatal diagnosis or screening for common indications

During pregnancy, obstetricians take care of the health of the mother-to-be as well as of the health of the fetus. Part of this care is non-invasive prenatal diagnosis such as ultrasound follow-up to appreciate the normal development of the fetus and maternal serum tests allowing risk calculations for trisomy 21 (Down Syndrome). When indicated, invasive prenatal diagnosis will be offered in order to allow for therapeutic interventions or termination of pregnancy. Via chorionic villus sampling or amniocentesis, fetal tissue is obtained and appropriate tests can be performed to diagnose a possible genetic anomaly. The three main indications for either high risk or low risk invasive prenatal diagnosis are: (1) a known recurrence risk of 50% or 25% for a specific genetic abnormality based on the medical history of the couple/family (such as a first child with mental dysfunction due to specific mutations seen in Fragile X syndrome, for example); (2) multiple malformations seen at ultrasound such as brain-cardiac-renal anomalies which are often caused by a chromosomal or gene anomaly; (3) age related or increased risk for Down syndrome based on maternal serum tests, which is by far the most common reason for low risk invasive prenatal diagnosis. Certainly in the case of ultrasound abnormalities, invasive prenatal diagnosis using microarrays is becoming the first choice method despite the presence of unknown or yet unidentified copy number variants indicating a possible anomaly in the genome (Wapner 2012). Once again, as described above, many more causal genetic anomalies can be detected when compared with current tests such as the karyotype to identify chromosomal anomalies. Data resulting from the use of microarrays for low risk prenatal diagnosis or rather screening for common indications (such as maternal age) recently became available inviting speculation that the technology may find its way to almost all cases of invasive prenatal diagnosis (Fiorentino 2012).

Certainly when microarrays are used to identify a genetic anomaly in a fetus with malformations before birth, the analytical validity has been proven because, again, the same and more abnormalities than those found in the past by performing karyotypes are identified. Moreover, clinical validity and utility have been established because the question asked by the clinician is answered and further action becomes possible to a certain extent. However, introducing this technology into routine clinical practice in the case of ultrasound abnormalities, emphasizes the need to counsel patients and for written informed consent. The pros and cons of the technique must be explained especially concerning the potential for unsolicited findings, which in some cases may be of uncertain significance (VOUS). Patients need to be asked the level of information they want to receive. In other words, the parents-to-be should be informed that the test may be able to establish

a firm diagnosis providing prognostic information on the health of the baby to be born enabling a decision to be made concerning further management of the pregnancy, including the possibly of termination. On the other hand, the parents should also be informed about the fact that no abnormality could be seen or that an abnormality could be seen which is clearly not related to the malformation but could be of significance for the health of the baby, or that the abnormality seen could also be of unknown significance (Vetro 2012). Taking into account the limitations of the test, analytical validity and clinical validity are proven. Clinical utility may, according to the test result, remain limited.

Non-invasive prenatal testing for gender diagnosis or for aneuploidy screening

Invasive prenatal diagnosis by chorionic villus sampling or amniocentesis as discussed above entails a risk of miscarriage due to the procedure. In some cases, the woman may lose the pregnancy despite a normal test result. Many efforts have therefore been made to develop non-invasive prenatal tests to replace the invasive ones. For many years scientists have tried to develop non-invasive prenatal tests based on isolating and analysing fetal cells from the maternal circulation. It is only recently that, on the basis of these long-standing efforts, non-invasive prenatal testing based on the analysis of cell free fetal DNA has become available as a clinically proven option. The first approach was to detect DNA from a Y chromosome – because of the certainty this was not coming from the mother. Nowadays, non-invasive prenatal testing based on the analysis of Y-specific sequences from cell free fetal DNA is in certain countries the method of choice to determine the sex of the fetus in the case of sex-linked conditions (an invasive test is only performed if the fetus is a male). Another situation where this non-invasive diagnostic test has proven to be valid is in the case of rhesus incompatibility. For monogenic conditions NIPT (Non-Invasive Prenatal Testing) is being developed as a diagnostic test (Bustamante-Aragonés et al 2012).

An apparently promising methodology for aneuploidy screening by counting chromosomes and more specifically, chromosomes 21, 18 and 13, has recently been developed (Hill 2012). The National Society of Genetic Counsellors (NSGC) currently supports Non-invasive Prenatal Testing/Non-invasive Prenatal Diagnosis (NIPT/NIPD) as an option for patients whose pregnancies are considered to be at an increased risk for certain chromosome abnormalities (Devers et al 2013). Also, the American College of Obstetricians and Gynaecologists supports this new procedure as a screening tool for fetal aneuploidy (Committee Opinion 2012). The position statement of the Board of the International Society for Prenatal Diagnosis is somewhat more cautious but recognizes the value of this new and rapidly evolving technology (Benn et al 2013). Although companies are already selling the test as a prenatal screening procedure in the USA and in Europe, no regulation framework or provision guidelines are yet in place to implement this promising technique in a proper way.

Many diagnostic accuracy studies have been performed in the last 15 years, and most of these have taken place in the last 3 to 5 years. A recent systematic review, as well as the position statements of the International Society for Prenatal Diagnosis, conclude that with a well-chosen technology, performed in the best possible conditions, the analytical validity is high with a high sensitivity and a high specificity (Mersy et al 2013). The National Society of Genetic Counselors (NSGC) urges that NIPT/NIPD be only offered in the context of informed consent, education, and counselling by a qualified provider, such as a certified genetic counsellor. Patients whose NIPT/NIPD results are abnormal, or who have other factors suggestive of a chromosome abnormality, should receive genetic counselling and be given the option of standard confirmatory diagnostic testing (Devers et al 2013). The American College of Obstetricians and Gynaecologists further states: Cell free foetal DNA testing should be an informed patient choice after pre-test counselling and should not be part of routine prenatal laboratory assessment. Cell free foetal DNA testing should not be offered to low-risk women or women with multiple gestations because it has not been sufficiently evaluated in these groups. A negative cell free foetal DNA test result does not ensure an unaffected pregnancy. A patient with a positive test result should be referred for genetic counselling and should be offered

invasive prenatal diagnosis for confirmation of test results (Committee Opinion 2012). Taking into account the use of previous non-invasive screening tests to detect aneuploidy prenatally, this new methodology should reach a high clinical validity and utility. However, large prospective studies in the first trimester of high-risk pregnancies and low-risk pregnancies are still required along with cost-effective evaluations.

Microarray or SNP array to predict risks for common diseases

Common diseases refer to conditions such as diabetes, vascular diseases, dementia and many others affecting a large percentage of individuals in an adult population. Based on research data, these diseases are considered multifactorial, meaning that an individual may develop the condition because of a genetic predisposition interacting with the environment. By comparing DNA sequences from affected individuals with non-affected ones using microarrays or SNP arrays, predisposing sequence variants have been identified next to protecting sequence variants. From these observations, risks to develop a disease can be calculated. Interestingly, these risks are prone to change and may decrease or increase with additional information becoming available. Research in this area is ongoing and far from conclusive.

Concerning the use of microarray or SNP array to predict risks for common diseases, several expert opinion papers state clearly that although the analytical validity of the tests is usually high because the genetic variation is correctly identified, the clinical validity and utility have not been proven at all. Moreover they wonder how one will be able to do this because of the need for a long time follow-up of a lot of data for a high number of individuals (van El and Cornel 2011). Nevertheless, despite the lack of clinical validity and utility, these tests are directly offered to consumers by private companies and could have an effect on health care systems. In conclusion though, while the analytical validity is usually high, the tests are so far of no use in the clinic, or for the individual who might want to know.

2.4 Examples of tests likely (or not likely) to be introduced in the near future

In the next paragraphs we will examine the (potential) validity and utility of new genomic tests that might be translated into a variety of health care settings in the near future.

Newborn screening

Newborn screening (NBS) was initially introduced many years ago for Phenylketonuria. This is an inborn error of metabolism - a hereditary condition - which if not treated from birth, will lead to severe mental retardation. When treated very early in life with a specific diet, the child will develop normally. As soon as these facts became clear, a test was developed to screen all newborns. If the test is positive, a diagnostic test is performed before taking action. Over time, more diseases, all rare, have met eligibility criteria for neonatal screening. Besides metabolic diseases, endocrinological deficiencies such as hypothyroidism, and other conditions such as cystic fibrosis and hemoglobinopathies are now part of NBS programs in certain countries. The critera to be eligible for NBS are that the condition is an important health problem, treatment is available, and a suitable test is available accepted by the population.

A recent survey done in Europe showed that the number of diseases for which NBS is performed varies widely per country or per region (Burgard et al 2011). NBS is not yet equally accepted and implemented at the European level today. And one should keep in mind that all screening programs although intuitively beneficial, do harm to a certain extent despite the fact that the aim of screening programs is to reduce morbidity and mortality (Cornel et al 2011: EU-expert opinion document). This document describes in detail why, how, and for which conditions screening should be implemented in European countries. Taking into account what we know today about whole genome sequencing, targeted whole genome screening (WGS) (for a panel of well-chosen diseases) could be envisaged based on the criteria used or suggested today to develop a screening program. Targeted sequencing

means that you limit the analysis to the genes of interest without generating unsolicited information. Using WGS to screen the neonate, one could think of keeping the whole genome sequence of the newborn somewhere and interrogate/analyze the sequence later with respect to a specific question or as a result of new insights leading to screening beyond neonatal screening, such as screening for breast cancer with BRCA analysis (Bowen 2012; CDC priorities). Screening principles are universal, which means that a European guideline document is useful, in describing why and how such a program should be developed.

Before applying targeted WGS in the context of neonatal screening, the analytical validity of the test has to be established by comparing this new approach with existing test procedures . In other words, does the new test identify the metabolic defect(s) that are identified by the existing tests? Clinical validity and utility of newborn screening have been shown in the past. This means that once the analytical validity of the new test has been proven, it will be necessary to confirm its clinical validity and utility. If the sequence data of the neonatal screening are used later in life for other screening purposes as mentioned above, again the analytical validity, clinical validity and utility of tests have to be taken into account before implementing such screening. Furthermore, the implementation of screening is population dependent (frequency of disease plays an important role) and is society dependent (priorities in health care /budget). The technology used will not only depend on its quality but also on its cost (not only the cost of the test but also the cost of its consequences). Therefore health-economic studies are necessary.

Pre-implantation genetic diagnosis and screening

Pre-implantation genetic diagnosis (PGD), performed on 3-day-old embryos obtained via in vitro fertilization, was developed some 20 years ago as a very early form of prenatal diagnosis to help couples with a high recurrence risk of transmitting a genetic disease to their offspring.. Infertile couples needing IVF were of course interested, but even more so couples for whom termination of pregnancy was not an option. PGD today is very targeted and looks for a specific chromosomal aberration or a specific gene-mutation in embryos of at-risk couples. Analytical validity is high, clinical validity is proven, clinical utility is variable (patient wellbeing is improved if successful; the birth of an individual affected by a severe hereditary disease can be avoided). Guidelines for good clinical practice exist and laboratory accreditation is being accomplished (Harton 2011 a,b,c; Harton 2012; Harper 2010).

Pre-implantation screening (PGS) - aneuploidy screening of the embryo - has been developed and is being applied to improve the outcome of IVF and increase the live birth rate. This approach was based on the fact that embryos of women aged under 35 and more so aged over 35, often have the wrong number of chromosomes and these embryos may not implant or if they do implant, can result in a miscarriage. Unfortunately, in randomized controlled trials (RCTs) the live birth rates did not improve. Microarray technology for aneuploidy screening which allow for the detection of all trisomies or monosomies and even partial trisomies and monosomies, is now being evaluated at different developmental stages of the oocyte and the preimplantation embryo - the cleavage stage and blastocyst stage. Whole genome sequencing to detect mutations or chromosome anomalies in embryos is at the moment a technical challenge.

Several small studies claim that the analytical validity of aneuploidy screening with microarrays on trophectoderm biopsies is high and that the test is ready for application in the clinic. However, even if this new technology seems promising, well designed randomized controlled trials are necessary before offering it in the clinic. When its clinical validity and utility have been proven, one application may be to offer the test to women over 38 opting for IVF, to avoid the birth of a trisomic child in the first place. Moreover, if the test is efficient in selecting the best possible embryo to implant, it may be more widely used in reproductive medicine (Harper 2012). Here research and development is being done in private as well as in public facilities. Regulation and provision frameworks and

guidelines should be developed now in order to facilitate qualitative implementation in different member states according to their visions or priorities. Whole genome sequencing of a preimplantation embryo by analyzing a single cell or a trophectoderm biopsy currently encounters technical problems that in the future, might be overcome. But, will there be embryos left for transfer? How will an embryo for transfer be selected? Most probably, every embryo will present with one or a few recessive or disease causing mutations. Which one should be chosen for transfer (Hens 2013)? More basic research is needed in the first place.

Carrier screening

Healthy carrier screening for recessive mutations is performed in certain communities in order to counsel future parents and actively debated elsewhere. For instance programmes for Tay-Sachs carrier screening as well as a few other diseases occurring in Ashkenazi Jews have existed for a long time (Shneider 2009). Carrier screening for hemoglobinopathies is offered in different countries. Cystic fibrosis screening is advocated by some but not by others. Applying the new technologies in a targeted way to test for several recessive conditions at the same time may have advantages. A selection of diseases frequent enough in a given population may be the way to go. Except for the autosomal recessive conditions, X-linked recessive conditions may be added because female carriers have an increased risk of giving birth to an affected child irrespective of the genome of their partner. A possibility that might be envisioned is the combination of newborn screening at birth and carrier screening later in life by using the same sequence data at different points in time.

So far, carrier-screening tests of high analytical validity have been proven to be clinically valid. Clinical utility is a different matter. At the personal or familial level, clinical utility can be proven: if both partners of a couple are carriers, they can refrain from having children together or they can ask for prenatal diagnosis or pre-implantation diagnosis; all options to prevent the birth of an affected child. At the provider level the clinical utility may be a matter of cost effectiveness: cost of screening versus cost of care for affected families. Once the analytical validity of a new test, combining carrier screening for several conditions at once, has been proven, a thorough health economic evaluation within a given population/country should provide an answer in order to decide whether to offer it by public health services or privately only (as is now possible via direct to consumer testing - DTC).

Prenatal testing for common diseases

Prenatal testing for common diseases is at the moment not considered and should not be considered because postnatal testing for common diseases is not, and maybe never will be, clinically valid or utile.

2.5 Conclusions

Looking at the cited examples, the existing QA frameworks that are increasingly being applied today seem solid. It is clear that before implementing a new genomic test in the clinic, research data need to be robust. From the examples discussed in this section (table 2.1) we may conclude that the analytical validity as well as the clinical validity and utility of microarray testing, postnatally and prenatally in the case of malformations, has been established and are the method of choice for diagnosis because they are the most efficient. Nevertheless the modalities for their application in the clinic need further discussion because of the unsolicited or unknown findings. Non-invasive prenatal testing has been shown to be analytically valid and clinically valid but to demonstrate its clinical utility on a large scale, controlled – preferably randomised - trials are needed especially if applied to low risk pregnant women. The analytical validity of the new technology for newborn screening or carrier screening is established. Based on what is known today about newborn screening, the demonstration of clinical validity and utility will follow. However the context in which screening takes place has still to be defined. The clinical validity and utility of carrier screening may be more difficult to demonstrate. Offering the new genomic tests for post- and prenatal testing for common diseases is premature although it is offered commercially. Also, whole genome sequencing of a pre-

implantation embryo should only be done within the frame of research to answer specific questions. It is clear that assessments of tests are complex. Attention should be paid to the context in which a test is considered analytically valid, clinically valid and utile. For instance in one specific group of patients the assessment can be positive while in another group not yet or not at all.

A gap in the system exists between research and translation into the clinic at the public level. Research or private money can take care of developing a test and checking its analytical validity and clinical validity. To evaluate the clinical utility it is more difficult to find research money. Here a system to allow the correct translation to public health care should be available before the health care system covers a test.

Table 2.1 summarizes the current and future applications of GBIT that have been discussed in this chapter, and indicates their analytic validity, clinical validity, and clinical utility.

Table 2.1. Stages of Quality Assessment for Current and Future Applications in PHG

Tests	Analytic val.	Clinic. val.	Clinic. utility	Comments	To do
Postnatal Microarray MCA	+	+	+	Criteria/platforms to be used in clinic published	Monitoring; learn/improve by doing
Prenatal microarray	+	+	limited	Criteria to be used in clinic needed; pre- and post-testing counselling mandatory; IC	Start when ultrasound anomalies before generalizing
Non-invasive Prenatal testing for T21	+	+	?	On the market in Europe via USA	Clinical utility urgently to be confirmed in high risk populations first;
Microarray common diseases	+	-	-	On the market via DTC	Regulate and/or inform population
Postnatal New-born screening WGS	-	+(theoretical)	?	Can be envisaged	Regulate screening; Choose best technology
PGD + WGS	-	-	-	Too many unknowns	More research needed
Adult Carrier screening WGS	+	?	?	Can be envisaged; (already offered by DTC)	Regulate screening; choose best technology; Link to new-born screening?
Prenatal testing common diseases	-	-	-	No sense	Prohibit?

MCA(multiple congenital anomalies); WGS(whole genome sequencing);PGD(Pre-implantation genetic diagnosis)

3 Issues of quality assessment in the context of service delivery

Borut Peterlin

3.1 Introduction

This chapter discusses the organisation of health care provision as another crucial element in establishing a responsible and effective translation of GBIT in practices of public health care. As novel genomic technologies are introduced in a variety of health care settings, these developments will also have impact on genetic services. Several new genomic tests are already used in clinical practice in the area of monogenic and chromosomal disorders. Moreover, advances in public health genomics shift the focus of future public health from strategies to combat disease determinants that appear to originate outside the body, to host-specific; 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 genetic testing and 'omic' biomarkers might increase the relevance of genetic services to the general population.

All countries are experiencing an increasing gap between what can be done from a technical perspective to improve population health and the amount of funding available. Several challenges have been identified for the introduction of genomic medicine in health systems, including a lack of evidence of improved outcomes, deficits in provider and patient education, limitations in reimbursement, lack of investment in research for clinical translation and preparedness of health care system for change.

The development and implementation of quality standards for genetic services could make an important contribution to the rational approach to implementation of new genomic developments in medical systems. While quality standards are well developed for molecular and cytogenetic testing as well as for reproductive and newborn screening programs, quality assessment in clinical services is still developing.

We believe that the following policy issues need immediate consideration 1) investment in the development of existing genetic services and educational activities for professionals and lay public;
2) new public-private modes of interaction for the provision of genetic testing; 3) facilitation of nationally approved guidelines or legislation related to genetic services, especially in the area of commercialization of genetic services; and 4) support for development and implementation of new innovative modes of genomic services provision.

3.2 Quality assurance: development of current services and novel modes of genomic service provision

Traditionally, the focus of medical genetics services has been to provide genetic diagnostic and counselling activities to patients with rare, Mendelian-inherited or chromosomal conditions. While the organization of genetic services varies among and even within European countries, core facilities usually consist of genetic centres that generally provide both clinical and laboratory services (Godard et al 2003). Several international bodies have developed recommendations on quality issues related to genetic testing and genetic counselling.[16]

The goal of continuous quality improvement in healthcare is to improve patient outcomes while maintaining or optimizing costs. While these efforts are well developed for molecular and cytogenetic testing and laboratories, and for reproductive and newborn screening programs, quality

[16] http://www.eurogentest.org/fileadmin/templates/eugt/pdf/guidelines_of_GC_final.pdf

assessment in clinical services is still developing.

Current genetic services are facing the challenge of how to implement novel genomic technologies in the area of monogenic and chromosomal disorders in clinical practice. Although individually rare, these genetic disorders affect about 7% of European citizens and consequently present an important public health issue. The introduction of new genomic technologies has important consequences for improving efficacy and understanding of molecular mechanisms which could lead to improved therapeutic strategies. Consequently European health systems are facing increasing demand for expansion of genetic testing and genetic services provision.

Several challenges have been identified for the introduction of genomic medicine in health systems, including a lack of evidence of improved outcomes, deficits in provider and patient education, concerns about privacy and discrimination, limitations in reimbursement, lack of investment in research for clinical translation, inter-professional and inter-organizational communication and preparedness of health care system for change (Williams 2009, Battista et al 2012). Policymakers' efforts meet with several types of resistance including political (professional hierarchies protecting their own interests), cultural (lack of understanding with which to bridge the gap) and scientific (knowledge difficult to articulate and present to non-geneticists).

Policy issue: Investment in the development of existing genetic services and educational activities for professionals and lay public might substantially improve medical services and quality of life in patients and families with rare genetic diseases.

3.3 Commercial genetic services: need for compliance with quality standards

Running parallel to developments in genetic testing and services integrated within health systems that are covered by social insurance programmes, private companies have established commercial direct-to consumer (DTC) genetic testing services. Genetic testing is offered for monogenic genetic disorders, more often for susceptibility variants associated with common complex disorders, and most recently for genetic screening in the framework of preconception genetic testing with screening for mutations in children and adults. While DTC genetic tests have typically been marketed and sold directly to the consumer without the supervision of a healthcare professional, the provision model has been modified so that that consumers must now contact a health care professional before being able to order the genetic testing service (Howard and Borry 2011). However, consumer interest in these tests has remained low so far – several pioneering companies have already closed their doors.

Evidently, commercial tests can also be assessed for analytic validity, clinical validity and utility, but there is a lot of debate on who decides the thresholds for deciding whether the test is predictive enough and useful to take. In a free market economy, the one who pays for the test can decide whether it is useful. Consumers might still be interested in the test, knowing there is nothing that can be done to prevent the disease (low clinical utility), because the perceived utility from undergoing testing reduces anxiety and stress. Such a test would never be offered in regular health care, where evidence-based criteria require clinical utility, but in the commercial domains these restrictions do not apply.

But even in a free market economy, it may not be desirable to leave commercial DNA testing unregulated or regulated by consumer protection laws alone. An adverse consequence of commercial DNA testing occurs when consumers seek follow-up testing and examination in regular health care. When tests have insufficient clinical validity or utility, follow-up examinations are often unnecessary and unjustified, and will increase health care costs. To date, these testing services are not well regulated, and harmonization of regulation of the international market of commercial DNA testing between member states is warranted.

Therefore several professional societies have developed recommendations related to the quality of DTC provision. In 2010 the European Society for Human Genetics (ESHG) published a statement with a number of recommendations: the clinical utility of a genetic test should be an essential criterion; laboratories should comply with accepted quality standards, including those regarding laboratory personnel qualifications; information about the purpose and appropriateness of testing should be given before the test is done; genetic counselling appropriate to the type of test and disease should be offered; and nationally approved guidelines considering all the above-mentioned aspects should be made and followed (ESHG 2010).

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

3.4 The current state of indicators, guidelines and regulations relevant to the quality of genetic services

Quality indicators including referral communications, follow up plans, appointment availability and patient satisfaction surveys, have been proposed for clinical genetic services at the international level (Zellerino et al 2009). Outcomes to measure the impact of genetic services have been proposed in the following areas: knowledge and information, financing, screening and identification, diagnosis-treatment-management and population health area (Silvey et al 2009). In terms of developing evidence-based guidelines in the field of genetic medicine, several difficulties in extracting evidence from the clinical genetics literature include the lack of randomized controlled trials, and small numbers of cohort and case–control studies were identified (Toriello and Goldenberg 2009).

In addition to the establishment of professional guidelines, regulation contributes to the implementation of quality standards for genetic services. A lot of regulation related to the quality of genetic health services in Europe is established at a national level. Nevertheless, few countries explicitly regulate genetic testing and counselling. On the other hand, there are some European statements that relate directly or indirectly to the provision of genetic services. *The Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Genetic Testing for Health Purposes* contains provisions to guarantee the quality of genetic services in Member States of the Council of Europe, in particular stating that a) genetic tests meet generally accepted criteria of scientific and clinical validity; b) a quality assurance program is implemented in each laboratory and that laboratories are subject to regular monitoring; and c) that persons providing genetic services have appropriate qualifications to enable them to perform their roles in accordance with professional obligations and standards.[17]

As genetic tests fall under the broader statutory regimens for the regulation of medical devices, they are subject to regulation by the EU IVD Directive that governs the safety, quality and performance of devices. This define requirements for placing a product on the market, production, labelling, clinical evaluation/investigation and post-marketing surveillance.

In 2011 the 'clinical/medical genetics specialty' was officially recognized as an EU-wide specialty which contributes to the quality standards of professional training in the area of genomic medicine.

Moreover, following the EU health strategy which focuses on strengthening cooperation and coordination, supporting the exchange of evidence-based information and knowledge, and assisting

[17] http://conventions.coe.int/Treaty/en/Treaties/Html/203.htm

with national decision-making, the Council of the European Union adopted a recommendation on action in the field of rare diseases.[18] A considerable part of medical genetics concerns rare diseases and about 80% of rare diseases are genetic. Accordingly, an EU Committee of Experts on Rare Diseases (EUCERD) endorsed a set of recommendations on quality criteria for centres of expertise for rare diseases in member states with the aim of helping member states in their development of policies concerning national plans and strategies for rare diseases in the context of the organization of healthcare pathways at national and European level (Khoury et al 2009).

Additionally, the EU released the Directive of the European Parliament and of the council on the application on patient's rights in cross-border healthcare which aims to establish rules for facilitating access to safe and high-quality cross-border healthcare in the Union and to ensure patient mobility (Peeters 2012).[19]

Policy issue: Facilitation of European and nationally approved guidelines or legislation related to genetic services, especially in the area of commercialization of genetic services.

3.5 Challenges in the development of quality assessment of future genetic services

Several models have been proposed for dealing with new challenges in public health genomics. Strengthening and modernizing the existing genetic healthcare service has been proposed in the UK, by expanding the workforce within specialized genetics services and investing in genetics training and information and communications technology budgets.[20] Individual patients would have access to services at the central location through satellite clinics or through telemedicine services (Kaye 2012). The need for more genetic counsellors and genetic education has been raised in a recent United Health group report (United Health 2012).

Multidisciplinary specialist clinics and coordinated services appear to be key to delivering proper care in rare genetic disorders. For several medical areas, inter-professional collaboration between geneticists and other specialists has been favoured. Moreover, there is also a tendency toward the integration of genetic services directly into primary care (Battista et al 2012).

Advances in public health genomics shift the focus of public health from strategies to combat disease determinants that appeared to originate outside the body, to host-specific 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 genetic testing and 'omic' biomarkers, might increase the relevance of genetic services to the general population. New approaches of genetic testing that may be introduced in practice in the future include expansion of universal screening for diagnosis of rare genetic diseases, risk-based genetic screening for diagnosis of predisposition to more common conditions and future health problems, as well as pharmacogenomic testing to assess the effectiveness or adverse effects of medical therapies.

In contrast to monogenic and chromosomal disorders, translation of human genetics and genomics related to common disorders is still in its early stages and there is a risk of generating too high expectations of the application of genomic medicine. The European Society of Human Genetics have developed recommendations for genetic testing of common disorders in a public health framework.

[18] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:C:2009:151:0007:0010:EN:PDF

[19] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2011:088:0045:0065:en:PDF

[20] http://www.publications.parliament.uk/pa/ld200809/ldselect/ldsctech/107/10707.htm

These stress the importance of the evaluation of the clinical utility of genetic testing for common disorders before large scale applications; prioritization based on cost effectiveness; and the need for sufficiently qualified health-care professionals and adequate regulation, among others (Van El and Cornel 2011; Becker et al 2011).

Models and initiatives have been established to evaluate and assess evidence about emerging genomic tests like ACCE model (analytic validity, clinical validity, clinical utility and associated ethical, legal and social implications), EGAPP (Evaluation of Genomic Applications in Practice and Prevention) and pharmacogenetic initiatives (Khoury et al 2010; Teutsch et al 2009; Hodge et al 2007).

The European Commission recently funded The Public Health Genomics European Network (PHGEN II) project (2009-2012) through EU DG SANCO (European Union Directorate-General for Health and Consumers) and EAHC (European Agency for Health and Consumers). The aim of the project was to develop European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies to support Member States in working together at a European level to address the challenges deriving from emerging genome-based information and technologies and to prepare for the paradigm shift of personalized healthcare over time. On 19 and 20 April 2012, experts from across the field of public health genomics representing key European and national organizations and institutions from policy making, academia and private sector, officially endorsed a summary of the best practice guidelines in 'the Declaration of Rome 2012'. The main responsibilities for public health authorities defined by the Declaration of Rome are to research, monitor health, diagnose and investigate, inform, educate and empower, mobilize community partnership, develop policies, enforce laws, provide care, ensure a competent workforce and evaluate genomic based information and technologies (Brand and Lal 2012). As a next step, a Joint Action 'Public Health Genomics and Personalized Healthcare: Implementing the "European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome-based Information and Technologies" in rare diseases and cancer' is planned as the next DG SANCO project. The planned Joint Action is designed to help Member States who are currently under pressure to define the right balance between providing universal access to high-quality genomic health services in a cost efficient way.

Policy issue: There is a need for support for development and implementation of new innovative modes of genomic services provision.

4 Implementing public health genomics: a look into the future

Iñaki Gutierrez Ibarluzea

4.1 Introduction

Different organisations have published future visions of Public Health Genomics and its implications in Public Health practice (PHGEN II, PHG Foundation, ESF). Although there is common agreement on its definition, as described in the Bellaggio statement that was signed by the main actors in the field, there is a diversity of visions on its implementation in reality. Several research initiatives (Hunt, ITFoM, OncoTrack) are trying to provide high quality evidence to introduce Genomic Based Information and Technologies (GBIT) in practice. In this chapter, we will discuss the challenges for quality assessment and regulation of approaches envisaged for the future and the high level of data integration that GBIT entails, including the combination of genetic data, clinical records, environmental and/or occupational exposures, as a basis for increasingly personalised, predictive, pre-emptive and preventive forms of public health genomics.

Existing best practices and guidance on quality assurance for genomic diagnostic tests are applicable to these new technologies; however these best practices (EGAPP, USPTF, HTA…) are unevenly used in different constituencies. In addition, research in progress is facing tight regulations (data protection), on the one hand, and weak regulations (medical devices approval in Europe) on the other. Any proposal to modify those directives should take genomic developments into account. Finally, new health care practices emerging from genomic developments should be combined with pieces of information obtained from different sources: environmental, life style and clinical records.

While we are establishing best practices and quality assurance mechanisms for the assessment of genomic diagnostic technologies, we are not applying similar practices to data obtained from other sources. This may lead to the generation of low quality combined evidence that calls into question the validity of the results and their implementation in public health practice. Therefore, the inclusion of GBIT in more comprehensive practices of data integration should be clearly based on evidence about its utility and affordability in health care in order to support processes of translation with real added value in terms of health outcomes. Thus, high quality data integration and its evaluation through transparent, reliable and robust analysis to support decision making, such as HTA, seem to be crucial to ensure a sustainable implementation of GBIT in real practice.

4.2. Challenges of translation of GBIT in future practices of public health genomics

There are at least three different reports and visions that address Public Health Genomics in practice directly or tangentially, including the report produced by the Public Health Genomics Foundation in 2010 (Burke et al 2010). A second report was produced and presented in 2012 in Rome, the result of a European Union funded project PHGEN II on Quality Assurance, Provision and Use of Public Health Genomics technologies. A third report was recently published by the European Science Foundation (2012). These three reports agree on the concept of Public Health Genomics as defined by the Bellagio Group on Public Health Genomics in the so-called 'Bellagio statement'. The results of the PHGEN II project were summarized in 2012 in the 'Declaration of Rome' which was endorsed by the Public Health Genomics Unit of CDC and the GRAPHInt group.

The main differences among these three reports are related to concerns about the implementation of these technologies in real practice. The Public Health Genomics Foundation emphasized the need for a strong evidence base for the implementation of new genomics technologies in health care practices. There are especially substantial gaps to be bridged in the field of bioinformatics in order to combine data of diverse origins (genomic, environment, occupational and clinical) generated from

studies tailored to different populations and settings. PHGEN II is more focused on methods and the Declaration of Rome, in the resume of its results, is more positive on the implementation of Public Health Genomics in the medium term. The prospective analysis made by the ESF report is the most futuristic approach to this issue. In this sense, it refers to different periods where actions would be implemented in real practice. Nonetheless, the three visions stated the need for research and evidence generation for this promising field.

The translation of technologies into practice follows a structured process that involves research, service provision (use in health care) and regulation (*see* figure 4.1). The process involves a set of *criteria* that support decision-making about what to invest in (*research and development framework*); the dimensions to be assessed to demonstrate the value of those technologies considered for health care practice (*provision framework*); and the norms that govern marketing approval of these technologies (*regulation framework*). The set of criteria established by each framework should contribute to a responsible and efficient process of translation. Although there are differences in the required criteria for these three frameworks among regions, countries and continents, there are accepted standards or best practices all around the world that aim to provide transparent, unbiased, robust, reliable and accountable approaches for decisions.

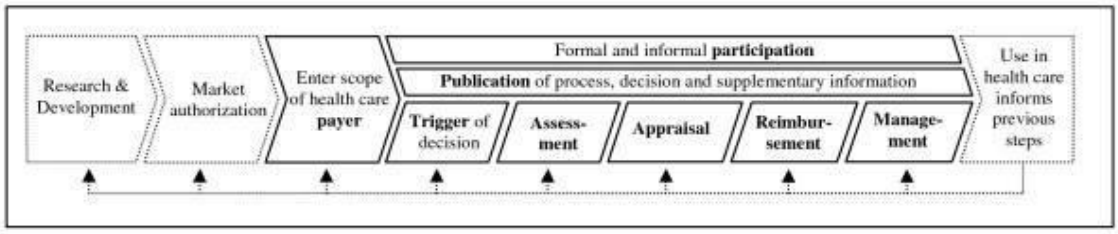


Figure 4.1 Different frameworks for decision-making within the process of translational medicine (Rogowsky et al 2008)

In the next sections, we will discuss the challenges that future GBIT practices in Public Health could face and the implications for the future shape of health care systems. The sections will focus on: (1) the challenges of research contributing to the aims of public health genomics, especially with regard to data integration; (2) the challenges of translating public health genomics research in (new forms) of health service provision, including transparent decision-making processes; and (3) the importance of quality assessment, HTA and regulation in shaping processes of translation in public health genomics practices.

4.3 Research

A defining feature of public health genomics will be its capacity to integrate complex information from multiple data sources and to generate a usable output to support the health of citizens and populations (ESF 2012). Nevertheless, in many occasions and cases this promising integration of data is only sustained at the research level and the complete integration will require that the data collection, handling and integration comply with the requirements of a well-defined design, research protocol, and unbiased performance of the research (including ethical, legal, social and economic considerations). Thus, there are initiatives in Europe, such as ECRIN (http://www.ecrin.org/) that are promoting the improvement of the quality assurance of performed research, enhancing and sustaining multidisciplinary and multinational research that in the case of the Public Health Genomics paradigm is crucial for further development and implementation in clinical practice. In this sense, the criteria used to measure and to critically analyse research will need further development to introduce Public Health Genomics. Special emphasis should be put on methods that explore the integration of high-quality data from different sources. Furthermore, the current pressure from personalised medicine and Public Health Genomics researchers and followers for 'in vitro' trials, that

comprise no human testing of health technologies, suggest, if successful, the need to review current levels of evidence tables (http://www.cebm.net/?O=1025) and study designs that better address health questions. In vitro trials aim to reduce the need of human testing by predicting patients' response to drugs and modelling their effects on in vitro subjects and groups, avoiding safety concerns and reducing costs. The key issue, critical for drug developers, is whether regulatory agencies will accept data based on their use.

Big population-based cohort studies, such as the HUNT study, have already included genetic data and are combining and integrating genetic data with data on the environment, lifestyle and from the clinic. They have already published studies on gene expression and environmental/lifestyle interaction that will lead to the design of Public Health interventions. However, many doubts about the integration of data from the quality assurance perspective are based on the accuracy of the source and the outcomes of the endpoints considered, especially in the case of environmental and occupational exposures. This has been common to classical Public Health Studies but for Public Health Genomics, accuracy of data for risk stratification and in vitro models is crucial. Models for the evaluation of public health interventions and quality assurance are available on NICE Public Health interventions and their measurement webpage.

Current EU-funded projects and patents (ONCOTRACK, ModCell™), try to combine genetic, epigenetic and clinical data on colorectal cancer as a model for further development and stratification of cancer patients and their management. Moreover, commercial platforms at affordable prices are already in place to lead to massively parallel sequencing (Illumina™). However, their value in clinical practice is still doubtful.

Given the requirements for data handling on the massive scale that this implies, we can say with confidence that Public Health Genomics as it is currently envisaged will not exist without advanced technologies, particularly in relation to *data generation and handling* (including bioinformatics). Genomics, epigenomics, proteomics, metabolomics, lipidomics, nutrigenomics and other 'omics' technologies, such as analysis of the microbiome, will be required alongside imaging and physiological monitoring to generate biological data. The challenge of data collection for personalised medicine is already beginning to be met by a series of biobanks that have been established throughout Europe. The importance of this work cannot be underestimated, yet it must also be recognised that this is only the beginning. This infrastructure must now be consolidated and expanded into an interoperable European network. To this end, it will be necessary to harmonise protocols for data collection and handling, address cross-border issues associated with data sharing and identify ways 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. This will need to be stored and, most importantly, integrated, analysed and interpreted. *Quality assurance will play an outstanding role in this process***.**

HTA could help in this process, as was pointed out by the General Directorate of Public Health of the European Union in the recent open call-for-tender EAHC/2013/Health/09, concerning pilots on early dialogue between health technology assessors and healthcare product developers during the development phase of medicinal products and medical devices. These 'early dialogues', however, should not only involve HTA bodies and product developers but other stakeholders such as regulators, professionals, patients, academia or managers, in order to establish a *collaborative process* to enhance the sustainable implementation of health technologies, including GBIT.

4.4 Provision

The introduction of Genome-based Information and Technologies (GBIT) into health care and public health should be based on a solid scientific foundation. Furthermore, a framework and process for

this translation should be established before the actual introduction of GBIT and the quality of the various parts of the process must be monitored throughout the period in which those health technologies are offered to the public. An important issue for this principle, as well as a recurring theme throughout this document is answering the following questions: 1) What will be the criteria (and the relevant thresholds) for reliability and validity? And 2) Who will be responsible to decide these criteria and implement the processes involved? (PHGEN II, Quality Assurance Guidelines, 2012)

As mentioned before, existing guidelines on the implementation of Genetic Tests in health care systems (Marquez-Calderon et al; GEN guideline 2006) clearly stated that the technologies should be implemented on the basis of three main criteria: *defined populations, clinical utility* and *organizational, economic and managerial capacity* of the provider to support the technology. However, responsible introduction of new health technologies into the health care system will always have to deal with this trade-off between a rigorous evaluation based on sufficient evidence on the new health technology and the timing of its introduction into health care. In the field of Health Technology Assessment this dilemma has also been coined: “It's always too early to evaluate a technology… …until suddenly it's too late.” by Professor Martin Buxton, Brunel University, London, UK [Buxton's Law].

Health Technology Assessment (HTA) is an existing practice for providing robust information and recommendations for decisions on clinical validity and utility and context-based affordability. HTA is a multidisciplinary process that summarises information about the medical, social, organisational, 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 seek to achieve best value (EUnetHTA and INAHTA definitions). HTA uses existing evaluation methods and best practices for clinical utility, as described in previous chapters (EGAPP, EuroGenTest, USPTF). However, HTA is not spread all over Europe. Some countries are lacking the expertise, while in others it is only supported by academia and not embedded in decision-making on health care provision. Therefore, existing HTA bodies should define common approaches to standards of assessment of GBIT based on previously discussed frameworks.

The need for homogeneous quality assessment processes in EU countries has been pointed out in several recently published documents (ESF 2012; Directive 2011/24/EU; CM/Rec (2010)11). In agreement with those directives and reports, there are initiatives in place to establish a permanent network on Health Technology Assessment in Europe (EUnetHTA) linked to other similar networks and organizations such as INAHTA, EuroScan or REDETSA. The implementation of the 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 the maxima of defined populations, clinical utility and organizational, economic and managerial capacity to provide these services (Marquez-Calderon et al; GEN guideline 2006).

Stratified screening based on genetic testing is an example of a radically new approach to prevention that is considered for introduction in established screening programs, as for example for colorectal, breast and prostate cancer (Dent et al, 2013; Dinh et al, 2011; Hawken et al, 2010; Chowdhury et al, 2013). Stratified screening strategies based on age, environmental factors and genetic risk would potentially improve the efficiency of screening programmes and reduce their adverse consequences. These strategies are based, in some of the cases, on risk stratification models (Wright and Dent 2011; Baird and Caldas 2013). To be suitable for use, a risk-stratification model must have adequate discrimination and calibration (accurately estimating the population’s average risk); it must also have clinical utility, which includes producing risk distributions for categories of people that are separated widely enough to justify different management of each category and so as to improve outcomes overall. Many risk alleles acting together may result in a distribution of risk in the population wide enough to be clinically useful for population stratification. Whether polygenic models will in fact

satisfy this criterion is uncertain, but this will need to be shown before the approach is implemented. Although the use of genetic information for population screening has great potential, we have to ensure that such screening tests will be beneficial (clinical utility) and affordable (health systems utility).

Finally, we have to consider that quality assurance of health care provision includes how the provision of services is performed (including data sourcing and data integration) and what knowledge professionals and citizens have about the process and its consequences. This latter aspect will affect the capacity of citizens to be engaged in a really informed consent procedure. Thus, current and future development of Public Health Genomics technologies and information will require accredited professionals, well-informed citizens and the reorganization of health care services as they stand today (Gutiérrez-Ibarluzea 2012). This will require the empowerment of citizens and health professionals and will multiply the requirements of shared decisions at the individual and population levels.

4.5 Regulation

The process of translating technologies from the research phase to actual provision sometimes requires the implementation of regulatory policies or laws that ensure that products that are market available comply with minimum requirements of safety and efficacy. While regulation for the market introduction of drugs in Europe is strongly defined and developed, including a quality assurance process by a unique body that gives marketing approval and establishes indications, this does not apply to medical devices.

One particular driving force for change in regard to *drugs regulation* is the potential reclassification of diseases (diseasesomes) and the application of new testing models, including whole genome sequencing. It has to be considered that up to now, health planning and management have been based on WHO International Classification of Diseases (current version ICD 10). Any radical change in this classification of diseases, as a result of GBIT, will affect health systems as a whole. In particular, the linking of drug licensing to specific diagnoses should be adaptable to changes in disease classifications, identification of new diagnostic categories, particularly those based around molecular pathways rather than organs and symptoms, and indeed to healthcare approaches that are not centred on specific diagnoses.

With regard to *medical devices* it is important to note that drug design is increasingly going hand-in-hand with the development of diagnostic tests to better define target populations. At this stage, it is of paramount importance that not only drugs but also accompanying technologies comply with best available standards of quality when they are receiving marketing approval and when they are finally considered for health care. The European regulatory framework for medical devices currently does not guarantee patients' and citizens' safety through proper scientific assessments of clinical benefits and harms based on clinical trials (whenever possible). Such regulations should adopt an improved marketing authorisation known from the field of pharmaceuticals. Sufficient pre-marketing data to assure that a medical device – including diagnostics – is safe and offers benefits for citizens is of central importance. The current system of Notified Bodies has been proven to be insufficient. Today there are 84 privately run Notified Bodies in the EU and it is up to manufacturers to choose the Notified Body to which they submit their application. There is no publicly available summary describing the basis for granting CE-marking, neither on the process – place of application, requirements for application, pre-defined criteria for decisions – nor on the results. It is not possible therefore for the rationale for an approval – i.e. efficacy and safety data – to be followed by the interested public.

Increased transparency is of paramount importance in any potential new regulation. Establishing an 'early dialogue, as previously mentioned, on the values that should be measured by regulators and combining information from different sources in a truly collaborative and multidisciplinary process, will help bridge the gap from regulation to provision. Sound evidence and its assessment in a process of HTA is a prerequisite to gauge and demonstrate innovation and to ensure appropriate decisions about the posterior coverage and reimbursement of new health technologies.

4.6 Conclusions and policy issues to consider

Current visions and initiatives are consistent in their views on the potential of Public Health Genomics for disease prevention and management and health services provision, nonetheless the expectations and considerations with regard to the *translation* of these technologies into practice differ.

At the *research level*, methods that explore the combination of high quality data and the possible role of 'in vitro' trials need to be considered as well as the promotion of the generation of data from different sources. Bioinformatics and its capacity are crucial to produce reliable combinations of data. In order to sustain innovation in the field, early dialogue is needed among different stakeholders, in which HTA could play an outstanding role.

At the *provision level*, that is the *organizational, economic and managerial capacity* of the provider to implement the technology in real practice, the spread of HTA practices is required for a responsible and effective translation of these technologies, including the assessment of clinical validity and utility of GBIT in agreement with previously described best practices and context based affordability along Europe.

At the *regulation level*, possible changes in the international disease classification, drugs marketing approval and medical devices directives in Europe need to be explored.

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Part III

Economic and societal aspects of Public Health Genomics

Report by Expert Working Group 3

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1. Introduction

1.1 Vision

Europe is facing increasing pressures on the healthcare systems of its constituent countries. These pressures arise from finite budgets that are often under downward financial pressures as a result of the current economic climate and from an evolution of health needs. *Chronic diseases*, that require permanent care over decades, constitute *the vast majority of diseases* affecting ageing populations. The *definition of health* has changed to include the larger *concepts of prevention and care*, including pre-birth prevention. The standard expectations of patients and public at large have risen.

To the visionary protagonists of genomic medicine, the results of the investment in Research and Development in the field of genomics at large, will be significantly enhanced health gain for patients as individuals and for the population as a whole. These gains will arise as a result of the development of personalised or precision medicines, where drugs and other therapeutic interventions will be increasingly targeted at genetically defined sub-sets of the patient population that are most likely to benefit, maximising disease reduction or cure and minimising unwanted side effects and other adverse events. Population health will, it is envisaged, also benefit as a result of improved preventative strategies, including screening programmes, and new methods for tackling common diseases and containing the resurgent threat from infectious disease pandemics.

These opportunities will, it is claimed, deliver greater efficiency, through maximising effectiveness and reducing cost pressures through the avoidance of secondary effects and the elimination of waste/inefficiency – which will allow further scope for resources released from current applications to be diverted to support the introduction of further innovation, thus creating a virtuous circle.

However, not all parties share this optimistic vision of the future. For many, the over emphasis on genomics will divert attention from other, cheaper interventions, and the genomic model of massive sequencing capacity accompanied by highly sophisticated algorithms to interpret the outputs is an over-simplification, in particular for complex and chronic diseases that constitute the major public health challenge. It can also be seen as a mechanism for directing public money to the private sector, through the allocation of scarce resources into therapies which will not significantly impact on population health, and which take efforts and money away from current practices or new alternatives still to be developed.

If genomics does not contributed significantly to reducing the disease burden of common chronic and complex diseases (heart disease, obesity, diabetes, cancer, mental health etc) then there is a concern that it will turn out to have been an expensive distraction, rather than the articulation of a new paradigm defining the future of health care. For genomic medicine to be able to claim to have made a real difference it must be able to show that it has improved the quality of life for patients and their families, and reduced the impact of their disease on the health care system and on society as a whole.

1.2 Challenges for Implementing Genomics in Healthcare

Changing medical practice is notoriously slow and difficult. *Medicine is inherently conservative* due both to the inherited and accumulative body of knowledge that represents current good practice and also as a result of the constraint to change imposed by the physical organisation of health care and the necessity of satisfying the demands of the regulatory system in all its complexity and diversity.

For a new way of working to gain traction in a health care system it must overcome the inertia created by existing custom and practice. This requires the system as a whole and the professionals

who work in it to reach a 'tipping point' where confidence in the necessity to change is sufficient to overcome the pressure to remain static. Bringing the system to and beyond this point will require investment in *developing skills and knowledge for those working in the system* so that they can deliver and interpret the improved outcomes for patient care that are envisaged, and an *infrastructure where both the 'hard' components* (the physical plant of the health service, industry and ancillary structures) and *the 'soft' components* (the regulatory framework) are capable of delivering, and there is the inherent capacity to accommodate change where relevant whilst also managing in historical way where genomics has yet to deliver or is an inappropriate strategy for addressing the problem at hand.

It will also be necessary to consider *the public and patient understanding* of the limits and possibilities of genomics in order to sustain trust and confidence in the system. Here, understanding of the possibilities will be framed by the creation of frameworks for the systematic interrogation and assimilation of new knowledge revealed through advances in research and development. But it would be a mistake to regard this too simplistically, and see the needs as a purely scientific and a medical shortfall. Development will often take place in a complex medical, economic, scientific and ethical framework, all elements of which will need to be addressed

Consider the example of non-invasive pre-natal diagnosis. Scientific advances in our ability to sequence free fetal DNA in the mother's blood have created a mechanism for the antenatal diagnosis of fetal abnormality. But as the box below demonstrates, this is far from a simply technical case.

Box 1 : Non-invasive prenatal diagnosis (NIPD)

At a scientific level, the development holds out the prospect of being able to provide a method for establishing whether or not a fetus is carrying the mutations responsible for genetic related disorders. As our scientific and technical capability grows, the list of disorders potentially testable for will grow. However, *at a clinical level*, for most single gene disorders, the presence of the mutations does not imply that the child to be will be severely affected (penetrance is never complete and disease outcomes are often variable). These ante-natal diagnoses can be made without risk to the pregnancy; however, an invasive procedure (as chorionic villi sampling or amniocentesis) is required in case of a positive outcome (false negative have also been described).

Access to NIPD while in pregnancy will give couples the opportunity to know whether or not they are going to have a baby probably affected by the conditions tested and consequently the opportunity to decide whether or not to continue the pregnancy or to terminate it. *Access to legal abortion varies* across the EU, with some countries (e.g. Ireland) making it difficult or impossible to opt for this, while others adopting a relatively liberal attitude with termination for fetal abnormality allowed when very early (e.g. the UK) or even late (e.g. France) in pregnancy.

Society, through the political process, the media, the cultural and religious institutions will frame the acceptability/reject for these new genetic tools. Views of patients affected by these diseases will also have to be taken into account. Take, for example, the case of congenital deafness. For many parents with no hearing deficiency, this can be seen as a disability that they might wish to avoid in their child, and the introduction of NIPD might lead to a decision to terminate the pregnancy. Many congenitally deaf people see themselves as a linguistic minority rather than a disability group, and they see the deaf community's culture as being as varied as that of any other minority in society. To them, categorising deafness as a disability, and one of sufficient severity to make termination of pregnancy, when it is detected, a legitimate choice, is a brutal eugenics policy.

More generally, questions on the limits of human selection at birth will have to be solved : which diseases to consider ? Can general criteria on disease characteristics and clinical validity of the

genetic mutations be fixed? How far have we to take into consideration the genetic of the population (and not only of the individual) when contemplating the possibility to eliminate a gene (e.g. what are the protective effects of some mutation such as cystic fibrosis?)

If the conditions for a socially acceptable introduction of NIPD are to be met, they will be influenced by *public health and economic factors*. NIPD could indeed be introduced as a testing service for families known to be at risk for a particular disease (family history of disease) or made available to all the pregnant women as a screening service (the way prenatal screening through ultrasound linked to CVS/amniocentesis is for a range of conditions in different member states). In the first context, single disorder tests would be more adapted (the only test proposed is the one corresponding to the disease with a particular history in each family), while the second context would favour the development of multiple mutations tests in which a fixed panel of mutations involved in a group of different disorders is tested in a single analysis. In every case, the conditions for real informed consent of the women/couples should be met. This has clear implication in the design, organization and costs of the programs.

Economic modelling for the introduction of such a service would have to take account of the cost of providing the service (infrastructure, personnel, specific training of personnel, consumables etc.), including the costs of counselling made available to women and couples in order for them to make really informed decisions. The cost of not offering these NIPD and so having to provide help by lifelong care for affected babies and support for their parents should also be quantified although they should not be the driver of the decisions.

These economic modelling would have to be based on the *screening procedure* chosen (at risk families only or all women). The business potentially generated by a generalization of the screening to all women and for a panel of disorders, could also be included in the economic modelling, since the firms selling the diagnostic kits will be inevitable lobbyists.

For *Public Health Agencies* responsible for population screening programs, the key question will be (assuming the reliability of the technology), does the cost of testing all pregnant women offset the cost savings associated with the avoidance of the birth of a number of severely impaired children, for each of whose lifetime care costs may add up to very substantial sums of money.

For *clinicians and society* the question may be framed in terms of whether or not this is a price we are willing (and/or able) to pay to bring this about.

1.3 Health vs Economy?

Analyzing the impact of genomic on health care should not go *without evaluating the effects that these technologies are expected to produce on the general economies of European countries*, at large and not only in terms of health economy. The tensions between health gain for all, and benefits for the economy, are present in many of the issues at stake. If health and economy may go together, this is not a systematic truth. Deciding to which extent the changes required in public health organization are good for health only, for the economy only, or for both, requires a good understanding and knowledge of the science, the clinics and the economic issues at stake.

Analysis of the economic impact is surrounded *by a context of strong uncertainty*. Genomics and its potential clinical applications represent a dynamic and rapidly moving field but they are also very uncertain. Some applications are very plausible since they are closely related to existing applications of genomic medicine but many others are much more speculative**.** *High promises tend to be all the more frequent that the investments required for many developments are very important*. In this context, *accumulating the knowledge required to assess the degree of realism* of these promises is

crucial. *Economic models* designed to inform public policies should *systematically consider different scenarios* in terms of promise fulfilling and of the time required to fulfill them**.** *Tools to deal with strong uncertainty in policy making* should be considered with interest (including SWOT analyses, collaborative decision making, etc.)

1.4 Outline of the report

The report is structured around the three main issues identified by the expert group as crucial in consideration of the possible economic and structural effects of introducing genomic-based technologies in the public health system:

1. ***Production of knowledge***. Forecasting the effects of introducing genomic-based technologies in the public health system is currently a very difficult task since so much information has not been produced yet. Consequently, we start the report with a section that highlights the knowledge to be funded in order to make strong predictions and recommendations. We also discuss the challenges at stake with the research and innovation model of genomics, including funding models, intellectual property at large and technology assessment.

2. ***Production of skills***. This section interrogates the implication on people skills, including education and training, manpower organization and staff planning and capacity building at large in society for public engagement.

3. ***Infrastructures*****.** This section discusses the changes anticipated in both the hard components (the physical plant of the health service, industry and ancillary structures) and the soft components (the regulatory framework) of the health care system, including the organization of new integrated technological platforms with corresponding secured data handling facilities, organization of diagnostic and clinical care, organization of screening policies and prevention programs, new regulations and models for market access and technology assessment.

2. Production of knowledge

2.1 Funding and producing knowledge for an effective introduction of genomic-based technologies in public health systems

Recent advances in genomics have been possible because of sustained and substantial investment in research and development from public, private and charitable sources. However to forecast if, how and at what cost, they *could be translated into tangible patient benefits, R&D funding needs to be complemented by investment in other areas.*

Many of these funding issues will be country specific, and as such are beyond the scope of this document. Some have been discussed by other working groups in the PACITA Project so do not need repeating here. *However it is appropriate to draw out some broad themes with a pan-European impact for consideration*.

2.1.1 Better knowledge on genomic-based reclassification of diseases and impact on the health system

A frequent claim associated with the clinical application of genomics implies that disease classification will move from organs to molecular defects. Diseases presently considered as different because they affect different organs could be unified on the basis of a common molecular defect. This claim is particularly frequent in oncology. The potential implications of such changes on the organization of public health are enormous. Hospital services, medical training, professional guidelines, health economy modeling, etc. would need to be profoundly restructured.

Accumulating good knowledge and data on the effectiveness of these clinical effects of genomics is of crucial importance. Funding should thus be dedicated to such studies, including clinical trials, to test the efficiency of reclassification, assessment of impact on the organization of health care, and identification of all possible consequences.

2.1.2 Defining valid procedures for quality assessment

For patients and professionals to have the confidence to rely on genomic data as a tool for securing health care improvements, *quality standards need to be developed and applied*. This is particularly the case with genetic testing services, where current regulations impose no requirement that diagnostic tests have either clinical utility or clinical validity.

All the quality standards have to demonstrate is that they measure what they claim to measure. Publicly funded projects such as Eurogentest (www.eurogentest.org) have developed quality assurance procedures for evaluating genetic testing laboratories, but these standards are voluntary.

The sustainability of any evaluation scheme will be based on the willingness of service labs in public sector hospitals to pay an inspection fee of some kind. This will represent an additional charge on already hard pressed budgets, and until the participation is QA schemes is made mandatory it is likely that coverage will be incomplete, leaving professionals unsure and patients vulnerable. For private laboratories offering over the counter genetic tests there is no regulatory framework – largely because many of these companies are situated outside the EU.

Creating a legislative framework to regulate the activities of these companies would be extremely difficult. Voluntary codes of practice, such as the one developed by the UK Human Genetics Commission, are a helpful way of highlighting what would be seen as good practice, but they lack teeth and are unlikely to be observed by those who are most likely to benefit from the operation of an effective regulatory framework. European legislation on devices and diagnostics is currently being revised. Whether or not this will address the issue remains to be seen at the time of writing.

2.1.3 Replacing genomic-based technologies in the general context of biomedical innovation

Evaluations of the application of genomic-based technologies to health-care should also be conducted from a broader perspective on biomedical innovation. Many developments are ongoing in healthcare and they cannot be all funded and implemented. It is therefore important to balance the possible health gains of genomics with that of these other developments in the health context of aging EU populations. Public health studies are needed and should be funded to deliver such comparative data.

2.2. Research and innovation in genomics

2.2.1 The model of Research and Innovation in genomics

Historically, in most EU countries, biomedical research and development were fairly clearly distributed between the public (including the charitable) sector and private industry, *following the traditional linear model of innovation*. Basic research into the fundamental biology of disease was primarily undertaken by academics working in universities and medical schools. Once these underlying mechanisms had been educated, and potentially 'druggable' targets identified, then the results were handed over to the private sector for the manufacture of novel products and for commercialization.

The culture and reward system of the two interested parties were significantly different: the public sector was driven by publication in high impact factor journals, whilst patent ability and commercial exploitation were seen as primary drivers for biopharmaceutical development.

In the recent context of genomic development, these clear boundaries have become blurred. University academics are encouraged to develop spin-off companies based on their own IP (intellectual property). Pharmaceutical companies are severely reducing their research facilities and tend to outsource it to academics. New funding mechanisms such as public private partnership (PPP) and joint ventures (such as the SNP consortia between a number of pharmaceutical and informatics companies and major charitable funders) are becoming increasingly common. The infrastructure demands of large scale biomedical research 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 elaborate data analysis and computational capacity that would be out of reach of all but a very few individual institutions or companies.

This evolution calls for the development of appropriate ethical and governance frameworks, capable of adapting to the new way of working. These include novel approaches to IP procedures (see below) and data sharing arrangements that are capable of crossing national and regional boundaries and incorporate material transfer agreements to permit simple exchanges between different jurisdictions and across sectored boundaries. All this will require political will – sustained across the EU and with other emerging players in China, India, Latin America and elsewhere.

This evolution relies on economic explanations on the driving forces behind economic growth. But it is not without implications for the effective diversity of subjects conducted in the biomedical research facilities. The closer links between academia and the private sector have important influences on the choices made for basic knowledge development. Research directions more likely to lead to short-term marketable products might be preferred over longer-term questions or studies that don't have any obvious short-term application. The actual proportion of academics really working with or for the private sector in PPP should not be considered as a good indicator of these phenomena since a leverage effect is going on. The research programs able to raise big money from PPP are often setting the agenda for many other smaller groups.

2.2.2 Will the model resist the market segmentation potentially generated by genomics ?

It is therefore very important to assess the extent to which this model will effectively be able to meet the specific challenges of introducing genomic-based technologies into the clinics, in particular for drug development, while maintaining a sustainable cost-effectiveness. Developing drugs relying on the genomic characterization of patients implies a segmentation of the market. A common disorder is disentangled 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. *The pharmaceutical industry is currently lobbying to change the rules applicable for drug access to the market and to develop new forms of PPP in drug development*. Their objective is a reduction of the drug development costs and the maintaining of a high profitability of the sector. *However these evolutions should not be made to the detriment of the health services of drugs or with a loss in cost-effectiveness*. The changes asked by the pharmaceutical industry should therefore be analyzed keeping in mind that public funding is now present at every stage of the research/innovation process. Public authorities are therefore entitled to take part in the decision process regarding profitability of drug developments. This includes novel approaches to Intellectual property (IP).

2.2.3 Taking a fresh look at intellectual property

IP arises from a contract between the inventor and society that allows for the generation of a return on investment as a reward for risk taking, providing certain rules are followed. *The application of IP in the context of genomics has proved controversial,* with strongly held views about the legitimacy or otherwise of the concepts. The introduction of the EU Directive on the Legal Protection of Biotechnological Inventions through patents was a long process that developed a remarkable amount of controversy and the adoption of fixed positions at opposite ends of a spectrum.

For some, gene patenting was and is fundamental to stimulate investment and the development of innovative therapies, for addressing unmet but potentially economically profitable medical needs. Gene patenting is considered as vital underpinning for the financial sustainability of biomedical research and development and a key to the European Knowledge Economy and future EU prosperity.

For others, patents in genetics are an attempt to privatize the essential underpinning of life. It is also a way to create monopolies that *limit the accessibility of genomic-based health technologies despite the fact that most of the research underpinning these developments was publicly funded*. Patents with exclusive licensing cancel out competition between labs and dramatically increase the costs of products.

Critics also *challenged the efficacy of gene patents as innovation incentives*. The information on genes constitutes a fundamental knowledge, potentially useful to many developments. Consequently, new research and innovation may rely on previous results all covered by a thicket of patents, with different patent holders. Accessing such information for innovation purposes requires a negotiation process with each patent holder at a potentially prohibitive cost. It has been pointed out that there would be risk of a 'tragedy of the anti-commons', in which innovation would be blocked by patent thickets.

Today the issue of IP in genomics is still a sensitive one. Patents are indisputably driving investments in the biomedical industry. However, since some patent holders have a very exclusive use of their patented knowledge, other firms have started to address critics on gene patenting, considering that '*gene patents potentially inhibit development and commercialization of products and technologies that look at many genes simultaneously' (Affymetrix).* Since many genetic developments now rely on multiple genes or sequencing of large regions of DNA (exome or whole genome sequencing), respecting all the patents is economically non-viable. Indeed many public sector molecular genetics

laboratories routinely ignore the fact that gene patents may be in operation relating to many of the conditions being tested for on the basis that enforceability of the patent by the patent holder is unlikely, due to the cost of enforcement, the likely payback and the potential for negative publicity that would be created by a vigorous process of enforcement.

While the protection of intellectual property on innovation through mechanisms that include the revealing of the innovation content (as opposed to securing it by maintaining secrecy) is essential to the exploitation of new genomic knowledge, it is *unfortunate that IP has, for many, become synonymous to patenting*. In our view *it is time to take a fresh look at the way in which IP is generated* and the use that can be made of various IP tools such as patent pools, copyrighting, open source licensing etc. to serve a range of benefits that may be societal as well as economic. Recently, a patent pool has been launched in the US for discoveries related to molecular diagnostic testing (Librassay). The patent pool proposes an alternative licensing, to foster "*widespread adoption of these important technologies, the lives they save and cost savings they can achieve*", in which access to multiple diagnostic related information covered by patents is organized through a one-stop license.

Other alternatives included specifically designed open source licenses. For example, the International HapMap Project was a large, publicly funded (NIH, Wellcome Trust and others) project that aimed to look at genetic variation between four distinct populations from different parts of the world. There was a very strong commitment by the researchers and funding institutions to making the sequence data generated publicly available. There was also a very legitimate concern that if the data was openly published on a web-site then unscrupulous operators might take chunks of it, add data of their own, patent the whole and lock it away for private advantage at the expense of the research community at large and at the cost to the funders of lost opportunities for future development. To avoid this, the raw data was made publicly available through a 'click-wrap' license, which applicants had to sign up before gaining access to the data. This imposed certified conditions included a prohibition on patenting these raw data. Such innovative uses of IP have served as a vehicle to promote non-commercial gains while securing the financial return on the investment.

IP has also been used to promote societal outcomes such as a low cost access to genetic tests for the population or the community that provides the resources or the money to make the research and development possible. In our view this is another example of a reconstruction of the role of IP, and the way in which it is to be generated and used in the future to promote innovation while securing access for all patients to beneficial outcomes potentially arising from genomic research.

The questions around IP and patents for genes, the way in which decisions are made about what is worth patent protection, and what should be publicly available for use, *might be considered a closed question in the EU since the related directives have been voted on*. We consider, on the contrary, that the evolution of genomics, 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'*. The applications of whole genome data will be made immeasurably more complex if there is a thicket of patents, each claiming ownership of discreet elements of the genome. This will inevitably push up costs, add complexity to the organization of health care and delay the appearance of novel interventions to the detriment of patients and to health care systems which, across the whole of Europe are struggling to meet the demands placed on the novel opportunities and rising patient expectations at a time of significant downward pressure on finances.

3. Skills and knowledge

The production and the maintenance of a skilled workforce in genomics is a crucial component for the successful introduction of genomics as a full part of future health services. Indeed, the resources and the quality of the workforce are the main components of any health service. Thus, if we want to implement and maintain genomics as a part of the provision of health services to the population, we will have to include developing an ambitious strategy of education and training.

A first step in developing the skills is to improve education and training in genetics in general and in medical genetics in particular for all health care professionals. The current status of genetic knowledge is likely to differ between countries, but seems in general to be rather basic. For most health professionals, medical genetics experience is likely to be restricted to monogenetic conditions with a high penetrance and a predictable course. If genomic medicine is going to be developed, the aetiology and the course of the related conditions are likely to have a more sophisticated pattern, including interactions between genes and environment, as well as between genes.

Another major change linked to the development of genomics is the reorganization of nosography. Common molecular pathways linking specific genotypes to specific phenotypes will be identified. These links will possibly be used to reorganize the classification of health conditions, suggesting new clusters of conditions conducive to new therapeutic and preventive strategies. It is a similar sort of rearrangement historically observed with developments in the concept of cardiovascular diseases (when coronary heart disease was linked with cerebrovascular disease through vascular pathology) or, more recently, with cardio-metabolic conditions (when diabetes and cardiovascular disease were linked through common risk factors).

Such reorganizations of nosography and its biomedical and clinical background have to be taught and trained. This has consequences on the structure of training infrastructure. Most hospitals are currently organised around an organ-based system of disease classification. If genomics is successful, the delivery of health care will be more dependent on molecular pathways, with similar approaches applied to different diseases previously thought of as unrelated and treated by different specialists. This will have consequences for the organisation of education and training.

Education and training relevant to genomic care have to be implemented at the undergraduate level, in specialized fields of medicine, and as continuing education. A successful introduction of genomics will promote new professions or at least new specializations within existing occupations. Because genomic care covers new areas of knowledge, and because this knowledge is in rapid expansion, a strong policy for continuing education is needed.

At the undergraduate level, students in health care have to be thoroughly versed with medical genetics. One aspect should be strongly developed: statistics and epidemiology. A large part of the development of genomic medicine has been (and will be) related to the use of statistics and population-based epidemiology. Some sort of an overall understanding on the quantitative models and epidemiological characteristics underlying the genomic knowledge is needed. Similarly, medical doctors need some understanding of physics, chemistry or cell biology.

If clinical care and the engagement with patients in the symptomatic exploration of their needs remains an essential component, the use of genomics by clinicians must be well integrated into the framework of care rather than the expansion of pure knowledge. This has to be carefully considered; the primary role of health care systems is and should remain so, to alleviate suffering, not deliver patients in a format designed to feed the research agenda and create the opportunity for economic prosperity.

4. Infrastructure

4.1 Changing the hardware of health infrastructures

Before commenting on the different aspects of health care infrastructure changes dictated by the introduction of genomics, we should start by recalling that *it is currently very difficult to predict the extent to which genomic information will effectively be turned into clinically relevant services*. There are loud voices supporting the inevitability of very rapid progress and subsequently pushing for fast evolution of the system. However, there is a real uncertainty on whether this technology will be able to effectively deliver accurate, useful and trustworthy benefits for a significant number of patients. This constitutes a real element of risk that should not be underestimated. Consequently, if the baby is not to be thrown out with the bathwater, there is a necessity for caution and a slow measured uptake.

4.1.1 Adapting clinical genetic infrastructures to big data production

Introducing genomic-based technologies in the clinic begins with *infrastructures able to efficiently produce genetic information.* This *activity is radically changing and will continue to change in the future*. *Traditional molecular genetics laboratories*, which are normally relatively small, have historically relied on 'in house', 'home-brew' techniques to look at single genes, one at a time, in search of a diagnosis. For rare conditions, kits are already available that are capable of examining growing batteries of mutation in one go. This *automation trend will continue* and the *development of high capacity whole genome sequencing facilities will potentially make traditional molecular laboratories obsolete in the coming years*. These new facilities will include the sequencing platforms, the computers and the storage capacities to process unimaginable quantities of raw data, specifically and accurately into clinically comprehensible formats.

This new 'big data environment' will also imply the implementation of procedures to guarantee the security of enormous quantities of highly sensitive data. The complexity of the information flows involved in these new procedures and the challenges that will have to be met to ensure a good quality of data while maintaining a sufficient level of security (necessary to get and keep the public trust) should not be underestimated.

4.1.2 Moving away from the organ-based clinical organization of health care infrastructures?

Most hospitals are currently organized around an organ-based system of disease classification. *It is possible that in the future, the delivery of health care will be more dependent on molecular pathways*, with similar approaches applied to different diseases that have previously been treated by different clinical specialists. *This will potentially have consequences for the way in which hospitals and community based resources are designed and developed*. However, the evolution in this process will have to be very cautious. Many diseases cannot yet be understood and treated on the basis of their underlying genetic pathology, and the historical, organ-based approach continues to be the only valid approach. The extent to which this shift from organs to molecules will be effectively clinically relevant is still a very open question.

4.2 Rethinking screening policies and prevention programs?

Public health will be affected by the introduction of genomic knowledge and technologies across the spectrum of its operation. One of the areas that will be facing significant changes in the foreseeable future will be *screening programs* – particularly prenatal, newborn but also adult screening programs including the genomic tests made during the incubation period of a non-communicable disease (e.g. diabetes), or before or during a treatment (e.g. genomic testing in cancer).

4.2.1 Neonatal screening

Neonatal screening is currently undertaken in many EU member states using a heel prick on a newborn baby to obtain blood spots for analysis. The number of conditions tested for varies from country to country, most of them without using genetic technology. The *selection of these conditions* is generally based on the application of distinct criteria (Wilson and Jungner) which *require an accurate, reliable test to be available at an affordable price for a condition for which there is an available and effective intervention*. Typically this might include disorders such as Phenylketonuria (PKU) where the inability of the affected infant to metabolize phenylalanine is addressed through a modified diet with the offending amino acid eliminated. With early detection and access to modified foodstuffs, the progressive mental impairment is avoided and the at-risk child is able to grow up with an unimpaired intellect and expect a normal quality of life.

Historically, the definition of an *affordable effective intervention has tended to be narrowly and medically defined*. 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 be reconsidered*. The value of information to couples about the future health states of their child has not generally been taken into account. Early knowledge might allow for the development of an effective care plan that might potentially secure the provision of timely interventions and support, leaving parents better able to cope, and affected children more able to avoid anticipatable deleterious developments. For example, in the absence of therapies that will alter the trajectory of Duchenne muscular dystrophy, an affected boy will normally transfer to a wheelchair around about the age of 12 years. This means he will need an adapted environment to preserve his independence and allow him a reasonable degree of mobility, thereby creating the potential for a social life roughly equivalent to that of his non-disabled peers. This adaptation of environment will also preserve his dignity by allowing him to be more independent in respect of everyday activities of daily living and provide relief to his parents from the demands of caring for an increasingly heavy and progressive disabled son. *This has physical and psychological benefits for the whole family and may serve the needs of the health service and social welfare systems* if the physical ability of parents to cope is sustained – by avoiding back problems through lifting an increasingly heavy offspring, or by avoiding family break up, for example. An early detection of Duchenne dystrophy could help the families to schedule in and budget for, the necessary adaptations in an appropriate and timely manner.

In the case of the Duchenne Muscular Dystrophy, the probability for a boy carrying a mutation to develop the disease is virtually one. In practice however, the situation is far from being clear-cut for most monogenic diseases, let alone complex diseases. *Unnecessary psychological burden for the child and his family, and economic and material costs for society and the family generated by the identification of mutations in a new-born that will not finally develop the disease (or develop a milder form), should consequently be taken into account.*

In the context of genetic tests for diseases with limited effective interventions, when the outcome of the test is a probability and not a certitude, or when the person that gives the consent is a parent or someone in loco parentis and not the patient himself, as in the case of newborn screening, *designing the procedure for really informed consent is a necessary but complex task*. As the range of conditions that are potentially screenable grows, this *issue might turn out to be intractable*. The conditions screened for will very likely be unfamiliar to the couples concerned, and even to the medical professional responsible for carrying out the heel prick test. 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 modeled in the costs/benefit evaluations of these programs.*

4.2.2 Prevention programs

The influence of screening programs based on genetic technology on the planning and organization of the health care system *goes well beyond the organization of prenatal/neonatal screening*. Prevention programs, intervention, monitoring and follow up programs could also be targeted to the individuals at greater genetic risk. A current example is provided by familial bowel cancer. In the absence of an identified gene, at-risk families were routinely monitored in many European Member States by regular colonoscopy. This is an unpleasant and potentially risky procedure, but it allowed for early detection and intervention when signs of change were detected. The identification of a gene involved in the disease led to the systematic genetic screening of at risk family members. Regular colonoscopies are then only proposed to the mutation carriers. *Global evaluations of such genomic-based targeted screening should include the savings of money and psychological burden related to the non-screening of the non-carriers, the costs of performing the genetic tests and also all the costs related to the circulation of a sensitive information (the genetic information) between different health care services* (from the platforms generating the data to the different services requiring the information). Further, the risk of disease among non-carrier members of high risk families might still be important, if the mutation tested does not fully explain the disease. Consequently, the reduction in clinical acts might not be systematically substantial.

Prevention programs, through the application of risk reduction and avoidance strategies, by behavioral changes or other techniques, *might be targeted to people at greater genetic risk*. This could mean an extension of risk charts widely used in clinical prevention, currently based on demographic and metabolic markers. Efficiency might be better since people could feel more concerned. One area where genomic data could have a substantial impact on the delivery of health care is in cancer screening and the development of stratified medicines targeted at genotypically distinct subsets of patients.

The consequences in terms of costs and organization of these new forms of targeted interventions are very complex. First, a central question is whether clear-cut categories of risks will be identified on the basis of the genomic information. When the risk of disease for the people not included in the genetically defined category of people eligible for a given intervention is not zero, alternative (or similar) interventions might be needed for them anyway. If genomic-based categories are poor predictors of health gain, the extra cost related to the genetic testing (which includes the realization of the test, treatment of information and communication of the test results with required explanation) might not be counter-balanced by the health benefits.

As already mentioned for screening, the setting up of such targeted intervention, including the delivery of useful and timely information to clinicians and families, *requires the storage and the analysis of a huge amount of sensitive data*. Related costs and organization include the maintenance of a bioinformatics data infrastructure, specific training for all personnel potentially involved in the use and interpretation of such data, and the procedures that will have to be set up to guarantee the security of such sensitive data. *The complexity of the information flows* involved in these new procedures and the challenges that will have to be met to ensure a good quality of data while maintaining a sufficient level of security (necessary to get and keep the public trust) should not be underestimated.

Public health programs for disease prevention might also be enhanced by our increasing ability to sequence the genome of pathogens. New vaccines could be developed using this newly disclosed genetic information. However, the costs and changes in organization required for this new information to be turned into more efficient strategies for pandemic avoidance go far beyond the simple costs associated with the virus analyses and vaccine development. The experience of avoiding the threatened pandemic associated with the H_2N_1 influenza virus, has highlighted the importance of new forms of international collaborations between public health agencies, the academic sector and

private industry, for these perceived threats to be efficiently addressed. Similarly, the development of new anti-microbial drugs necessary to fight the problem of multiple-resistant bacteria might benefit from the sequencing of their genome to identify new targets. However, since the market for such antibiotics is currently limited, *such developments have little chance to be undertaken by the pharmaceutical industry*, despite their possible urgent need in a near future - infectious diseases thought to have been conquered by antibiotics might will return if new antibiotics are not developed - *if new economic arrangements between the Member States and the pharmaceuticals industry are not invented*.

5. Regulatory framework

5.1 Regulation

This section aims at exploring the regulatory framework related to three interrelated areas of health care significantly influenced by the developments in human genomics. First, it addresses the challenges raised by the development of new medicines to the traditional regulatory system. Second, the normative framework to be implemented in clinical practice informed by human genomics is presented. Third, the broader social and ethical issues related to integration of human genomics and personalized medicine into the modern health care system are also briefly addressed.

5.1.1 New regulatory framework for clinical trials.

While most clinical developments for innovative products will be undertaken by industry, *the regulatory requirements that will need to be met impose significant cost burdens* in their own right. The need for change has been referred to elsewhere in this chapter, but securing this will require investment in training and retraining of regulatory affairs professionals both in National Competent Authorities, the EMA and in Industry. It will also potentially require *revision of the fee structure charged for the examination of dossiers prior to the granting of a Marketing Authorisation* in order to avoid undermining the economic viability of the regulatory agencies.

As has been pointed out in the previous sections, diseases fragment into genetically distinct subsets, and there is a danger that all but the largest of these will become untreatable because the economics of developing targeted therapies for smaller and smaller subsets will make the costs prohibitive. The pharmaceutical industry sometimes claims that the development cost of a new drug is around $1 billion or more. This figure includes the costs of failure, and the investment necessary to take the new product through the regulatory system. Although the cost of developing a drug for a rare disease, especially if this is done by a start-up or an SME may be less than this, nevertheless it can still be significant, resulting in a cost/patient treated in excess of $100,000/year or even substantially higher. So long as there are only a small number of drugs for rare diseases with a marketing authorization from the European Medicines Agency, these costs may be absorbable by national health care systems, but there will come a point where this is no longer the case and novel therapies will not therefore be prescribed and reimbursed no matter how effective they may be.

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’. Whilst it is in nobody’s interest to produce drugs that do not work, or are unacceptably dangerous, the costs of compliance within the current regulatory system are in danger of imposing a crippling burden that will stifle innovation, leading to persistent unmet patient need and damage to the economic competitiveness of EUplc. This is not to advocate for the abandonment of the regulators’ criteria of Quality, Safety and Efficacy as the basis for attracting a Marketing Authorisation on a novel therapeutic. Rather it is to state that the mechanism for determining whether or not a drug has met a need could develop in ways that enable regulation to follow biology, rather than by expecting biology to obey the law (no matter how neat it would be if this were to be the case).

Central to the creation of a new regulatory framework is securing patient engagement in the process. Scientific committees at the EMA have been influenced by the presence of patient representatives as full members, and as such have been able to modify their procedures to some extent. However, when looking at evidence of efficiency, there is often an over-emphasis on hard endpoints at the expense of other aspects of life that matter to those directly affected and their care givers. For patients and families, consideration of issues relating to benefit and risk will often include psychological and social dimensions in addition to physical and biological endpoints. Their willingness

to accept a risk will be influenced by the value they place on the anticipated benefit that a novel therapy is intended to provide, the availability of alternatives, and the impact that elements of the treatment have on their everyday lives. Recognizing this will help focus drug development programmes on issues that are important to end users, thereby influencing the willingness of patients to volunteer for trials and their compliance with the experimental regime, especially if this has been constructed in such a way that the research fits around the life of the patient, rather than expecting the patient to fit round the demands of the trial protocol.

Increasingly the traditional route to a Marketing Authorisation is a linear progression from pre-clinical studies, through phase 1, 2 and 3 of clinical trials, and after an MA has been issued, phase 4 pharmacovigilence. This system is currently bending under the stress of trying to cope with innovative medicines derived for genomic insights. Possible alternatives are emerging, but for them to be successful, regulatory practice will need to adapt, and public education will be necessary to ensure motivated support for the biomedical R &D process so reducing the risk of a public backlash in the event of significant adverse events becoming an issue.

One such model has become known as Adaptive Learning or Progressive Marketing Authorisation. This scheme proposes that phase 1 and 2 trials be merged, and if successful, then a 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. It is likely that a switch of this type in the regulatory process will initially find favour amongst patients for whom there is currently no effective therapy available. However, early use in patients would potentially be associated with significant risks, and careful consenting of the target population would be an essential pre-requisite.

Nevertheless, approaches of this nature offer significant potential for deducing costs of drug development making it easier to develop innovative products for (as yet) unmet medical needs, generating a sustainable future for the pharmaceutical and biotechnology industries without imposing an undue burden on publically funded health care systems.

In parallel with the evolution of the regulatory framework as described above it will be essential *to make the operation of Health Technology Assessment frameworks more able to establish the real value of innovative medicines to the patient and to society* as well as to the health care system responsible for the area of the patient hoping to benefit from a given innovation.

However, the system used to establish the cost burden or budgetary impact of a novel therapy must be robust, it must also be logical, comprehensible to the stakeholder group who have an interest in its operation, sufficiently comprehensive in respect of the factors incorporated into the equation used to determine cost and clinical effectiveness to carry patient and public legitimation, and appealable or renewable where there is a perception that a mistake has been made.

The rhetoric of HTA is unarguable. Of course health care providers need to know what works, for whom, under what circumstances, how many people are affected, the cost, and so on. The problem is in the practice of the appraisal process where too often, those who had hoped to benefit feel the process to have been flawed, and that they have been unreasonably denied their opportunity to have their health care needs met. As genomic advances deliver possible interventions for rare diseases and/or small subsets of common ones, so the methods used to evaluate their clinical effectiveness will need develop to take account of the benefits to be accrued. If not, there is a significant risk that the incentives provided by the Orphan Medicinal Products Regulations which has produced a dramatic upswing in the number of products under development since their introduction in 2000, will be nullified by the operation of a system of HTA that will inevitably deem them to be unaffordable, whether determined on the basis of cost/patient, budget impact or whatever.

5.1.2 Genomics and regulations of clinical practice

Ethical and legal challenges of human genetics and genomics have been actively discussed since the second half of the 20th century and even before, however there has been a lack of international regulatory standards in the field. The Additional Protocol of the Council of Europe (CoE) Oviedo Convention concerning Genetic Testing for Health Purposes adopted in 2008 (further referred to as 'Protocol on Genetic Testing') can therefore be regarded as one of the most important European (or international) legally binding instruments specifically dealing with the topic.

Most of the principles set up by this protocol are generally accepted in medical practice.
For the purposes of this report we will first concentrate on the principles relevant for the health care provider/patient relationship:

- clinical utility;
- respect for private life and the right to information (including the right not to know) and
- non-directive manner of counselling.

Principles relevant for the health care provider/patient relationship

Let us start with the *principle of clinical utility* which sets the context for other important principles and guidelines relevant for the communication between a health care provider and the patient or user of genomic related interventions. This principle combines the predictive value of the test and the availability of an effective therapeutic or preventative intervention related to the tested health condition. If clinical utility of the test or screening program is high, that is the high predictivity of the condition can be followed by an effective intervention, the implementation of a test or program might be seen as unproblematic. This is not, however, always the case because the programs of prenatal diagnosis for monogenic or chromosomal disorders can have a very high predictive value followed by such intervention as termination of pregnancy. The use and development of NIPD technologies described in previous sections of this report clearly demonstrate the problem. The further development of these technologies will presumably enable many more diseases of the fetus to be tested and predicted in the future. Taking into account research data showing that the most common outcome of prenatal testing with positive pathological findings is the termination of pregnancy, this question as well as the issue of eugenics may become even more visible. (For example, only 3 out of 164 pregnancies diagnosed with Down's syndrome were preserved in Australia; 95 percent of women in France found abortion appropriate in the case of trisomia 21; research in California found that only 1 out of 17 pregnant women carrying babies with Cystic Fibrosis decided not to terminate pregnancy.) The common practice of terminating pathological pregnancy is seen by some groups as discriminating in respect to disabled people and as a form of eugenics. The case of congenital deafness presented in this report illustrates the sensitivity and complexity of the problem very well because, as has been emphasized, many congenitally deaf people see themselves as a linguistic minority rather than a disability group.

Right to information and the right not to know is another important principle to discuss. In modern health care, patients are entitled to know any information about their health, including the purposes and results of genetic tests and screening programs. However, the discussion on the criterion of clinical utility indicates how complex the implementation of these rights can be, especially in the context of predictive uncertainty and/or limited therapeutic choices. For example, when genetic tests provide information about the probability of a child developing a disease without any preventative or therapeutic options. An example of testing for Duchenne muscular dystrophy reveals the problem in its full complexity: does the information for the couple that their child is going to develop a severe disease enable the family to prepare and adjust themselves with the prospective life changes or can it cause unnecessary stress and burden?

Several important issues should be addressed here. On the one hand, educational/informational efforts to understand the purpose and possible outcomes of the tests are extremely important. Secondly, the right to reject the test ('opt out') should be stressed. And, thirdly, the wish not to be informed about the results of testing should probably be considered even more seriously than in the routine clinical practice. It should be acknowledged that sometimes the patient's right not to know might conflict with the doctor's duty to provide care. It might happen that making a person knowledgeable about the results of a test is the only possibility for preventing the disease or delaying its development. An even more controversial situation can arise if a person does not want to know the results of the test that can have an impact on family members. This leads to another ethical dilemma, whether and under what circumstances the results of person's genetic test can be revealed to his or her family members.

Finally, it is important to stress yet another provision of the Additional Protocol. Its Article 8 requires that *genetic counselling should be given in a 'non-directive manner'*. This requirement is an expression of the principle of respect for personal autonomy which has already been presented as one of the fundamental principles of modern medical ethics. However, it should be taken into account that the idea of non-directive counselling as an attempt to avoid any influence or pressure on a person can be problematic in the context of personalised medicine. First, indirect pressure can occur because of the privileged position of a counsellor in terms of knowledge, experience and social status. Second, and more importantly for our discussion, the increased power of prediction, which is supposed to be achieved due to the developments of personalised medicine, can significantly increase this 'authority', with a doctor giving advice to the patient. Especially sensitive situations of this kind can arise with regard to reproductive choices that may include the termination of pregnancy.

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Part IV

Ethical, social and legal aspects of Public Health Genomics

Report of Expert Working Group 4

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1. Introduction

This report concerns the ethical, social and legal aspects of applying genetics and genomics in a public health perspective. Based on a critical evaluation of such applications it will raise critical policy issues and propose criteria and processes for the responsible translation of research results into clinical practice.

Although much has been published about the ethical, social and legal implications of human genetics and individual genetic testing, little research has be done up to now on the ELSI-aspects of genomics as applied in public health (public health genomics). One of the reasons for this may be that it is not always easy to clearly discern genetics from genomics and individual care from public health related measures. Because sound policy making relies on empirical evidence and ethical reflection, an urgent need exists for ELSI-research and studies analysing already existing or emerging implications of genomics for public health purposes.

The report focuses on health related applications of genetics and genomics and not on their usage for forensic, social or recreational purposes. However, it is sometimes difficult to draw the line between different fields of application: health related genetic research or testing might reveal non-paternity and life-style motivated testing may discover disease dispositions. Still, the report does not cover explicit non-health related genetic analysis and testing like the envisioned testing for athletic, aesthetic or social traits, ancestry and other forensic testing, social sex selection or tracing anonymous sperm donors. These issues will have to be dealt with elsewhere.

The report is structured into seven sections. *Section two* following the introduction covers conceptual aspects of public health and public health genomics. *Section three* depicts existing legal frameworks and challenges to existing ethical principles as well as professional, regulatory and legal frameworks. *Section four* explores and concretises problems that may arise by the travelling of personal data, which cannot completely be anonymised, between research and care; two fields of data production and usage which are structured and governed by partially different ethical and legal standards. *Section five* deals with commercial developments and interests in the field of genetics and genomics and *Section six* sketches a framework for responsible translation and implementation. *Section seven* concludes the report by summarizing its findings and recommendations.

2. Genetics, genomics and public health

2.1 New technical and scientific developments

At a press conference in 2000, the President of the United States (Bill Clinton), together with the researchers Craig Venter and Francis Collins announced the completion of the first survey of the entire human genome (Collins 2010). The expectation was that, "It will revolutionize the diagnosis, prevention, and treatment of most, if not all, human diseases". Up to then, clinical geneticists had focussed on analysing the genetic underpinnings of *rare* disorders, especially chromosomal disorders and monogenic diseases. After completion of the human genome project, genomic scientists hoped to elucidate the genetic underpinnings of common diseases. Common *single nucleotide polymorphisms* (SNPs) were thought to be candidates for genetic factors influencing the development of such diseases. In order to identify them in *genome wide association studies* (GWAS), large numbers of persons were involved in such studies looking at many variants in a hypothesis free approach (van Ommen 2008).

Genome wide analysis of SNPs and extensive sequencing are facilitated by the development of high throughput sequencing technology and computer assisted data retrieval, storage and analysis. As early as in 1987, the term 'genomics' was adopted for the newly developing discipline of DNA-mapping and sequencing. According to McKusick and Ruddle "The new discipline is born from a marriage of molecular and cell biology with classical genetics and is fostered by computational science." (McKusick and Ruddle 1987) Whereas genetics "refers to the study of genes and their roles in inheritance – in other words, the way that certain traits or conditions are passed down from one generation to another", the term genomics "describes the study of all of a person's genes (the genome), including interactions of those genes with each other and with the person's environment." (National Human Genome Institute.

One of the mayor drivers of genomics is technological progress. In the clinical context, the first individual genomes have already been fully sequenced in order to clarify the causes of diseases and pathological processes of unknown origin and aetiology. Ambitious projects are on the way that aim to sequence individual genomes or groups of people or whole populations. In 2008 the international 1000-genomes project started which aims at sequencing the genomes of 2,500 individuals in order to establish a detailed map of human genetic variations. By October 2012, the genomes of 1,092 people had already been sequenced (The 1000 Genomes Project Consortium 2012).

Together this creates a 'technology push' and a search for new applications of genomic technologies in the health sector, be it in individual care or public health. However, despite technological progress, scientific advancement and aggregation of big data, DNA-sequencing or genome wide analysis is currently being used mainly in research. There is still a wide and probably widening gap between the amount of information which can be created about the structure of individual DNAs or genomes on the one hand, and our ability to interpret these sequences and to understand what they mean and what kind of possible health implication structural alterations, mutations or single nucleotide polymorphisms may have, on the other. Furthermore, "GWA studies have identified hundreds of genetic variants associated with complex human diseases and traits, and have provided valuable insights into their genetic architecture. However, most variants identified so far confer relatively small increments in risk, and explain only a small proportion of familial clustering, leading many to question how the remaining, 'missing' heritability can be explained." (Manolio et al 2009)

This is why a decade after the completion of the human genome and the euphoria created by it, Francis Collins concluded in 2010 that "the Human Genome Project has not yet directly affected the health care of most individuals", but also that "we invariably overestimate the short-term impacts of new technologies and underestimate their longer-term effects". (Collins 2010)

While the latter is still controversial, it is clear that patients have experienced little progress in health care so far, although investments of financial and human resources have been huge. There are several reasons for this gap between amazing successes in research and somewhat disappointing clinical outcomes. For example, human biology turns out to be much more complex than had been anticipated before the completion of the human genome. Many of the newly identified genetic variants have a low predictive value and the clinical utility of most genomic technology applications still has to be proven.

The premature introduction of genomic technologies into the market and especially into the health care sector which is not well prepared for an appropriate use of genomic information, may create harm to patients and economic failures. Current regulatory frameworks do not specifically apply to the questions posed by this development. This situation constitutes an obligation for politics to supervise it and it generates a need for proactive policy in order to pave the way for meaningful services on the one hand, and to prevent unnecessary and potentially harmful applications which may create obstacles for further developments on the other.

2.2 Public health and public health genomics

With the advent of high throughput technologies and the increasing availability of knowledge about the workings of single genes and larger parts of the genome, the new scientific and technological developments started to attract the attention of actors in the field of public health. Some suggested that "Genomics should be considered in every facet of public health: infectious disease, chronic disease, occupational health, environmental health, in addition to maternal and child health." (Gerard et al 2002) Others envisioned that, "Sequencing of the human genome and the subsequent demonstration of variation in numerous genes in health and disease will surely stimulate a golden age for the public health sciences." (Omenn 2000: 1)

Such visions were the starting point of a debate on the role of genetics and genomics in public health. It has led to a movement pushing for 'public health genomics' (PHG): "The idea of integrating genomic knowledge into the aims and tasks of public health". (Brand 2005:115). An integration, according to Brand, that "will be one of the most important future challenges for our health-care systems." (ibid.)

Public health itself has been defined as: "The science and art of preventing disease, prolonging life and promoting health through the organized efforts and informed choices of society, organizations, public and private, communities and individuals." (Winslow 1920). Examples of traditional public health measures to achieve these goals are vaccination, distribution of condoms, sanitation and occupational safety. Due to its relevance for PHG, disease prevention deserves a special consideration. There are basically two approaches. Rose made a distinction between individual approaches and population approaches (Rose 1985). Individual approaches focus on identifying high-risk individuals and providing some kind of individual protection. The population approaches focus on identifying the underlying causes of disease and providing an intervention that alters the risk distribution at the population level (Burton et al 2013). These approaches may be complementary.

Until the turn of the last century, public health research mainly focussed on *external or environmental factors* like nutrition, infectious diseases, pollution or workplace conditions. During the last two or three decades, the perspective has broadened from individual behaviours and external risk factors to issues such as inequality, poverty, and education. It is recognized that health is affected by many different factors, including biological, environmental and socioeconomic determinants. With the advent of genetics and the growing efficiency of genomic technologies, DNA-sequences and genetic information as *internal constituents of the human body* involved in human

health and disease increasingly attracted attention and became the focus of some Public Health specialists assembling under the umbrella of PHG.

Although it has been discussed for some 15 years, PHG is still seeking its proper form and content. An important step was taken in 2005 by a group of experts from Canada, France, Germany, the UK and the US who met in Bellagio, Italy. This group defined public health genomics as: "The responsible and effective translation of genome-based knowledge and technologies for the benefit of population health" (Bellagio Report 2005). PACITA uses a somewhat extended version of this original definition: "The responsible and effective translation of genome-based knowledge and technologies into public policy and health services for the benefit of population health (see, e.g., Lal et al 2011).

We will take this definition as the starting-point for a discussion of the ethical, legal, and social implications of public health genomics. However, the definition needs some further comment.

(1) It highlights three different aspects of public health genomics: research, public policy and health services. Each aspect has its own ethical, legal, and social implications.
(2) The definition describes the relation between research, on the one hand, and public policy and health services, on the other, as 'translation'. However, translation is not simply an application or implementation of genomic knowledge but requires other kinds of knowledge: public health, medical, legal, organisational, ethical and so forth.
(3) The definition focuses on population health rather than individual health. In this regard public health genomics differs from community genetics. It is not clear, however, what this difference in focus entails. The approach of public health genomics requires a delicate balancing of public interests (collectivism) and the interests of individuals (individualism).
(4) The definition does not clarify what it means more precisely to 'benefit population health'. One option is to think in terms of the goals of traditional public health, namely health promotion and disease prevention. The problem is how 'genome-based knowledge and technologies' can contribute more precisely to these goals.
(5) By mentioning public policy and health services the definition indicates that the translation of genomics should be carried out through organised efforts of society. How this is achieved may vary among different countries depending on their types of health care system.
(6) By merely talking about 'genome-based knowledge' the definition neglects to mention explicitly the interaction of genes with behavior, diet and the environment, which are extremely important.
(7) It is vital to note that the definition is not purely descriptive but includes the normative and evaluative terms 'responsible' and 'benefit'. However, it does not explicitly mention equity, i.e. that the benefits should be 'accessible to all on the basis of their vulnerabilities and needs' (as stressed in the mission statement by the PHG Foundation 2013a).

In order to evaluate the ethical, legal and social implications of PHG, it is first nessessary to clarify whether there are similarities or differences compared with closely related fields such as clinical genetics, community genetics and traditional public health. In a second step, the relevance of these differences with regard to their ethical significance needs to be assessed.

a) PHG versus clinical genetics

Clinical genetics is the part of clinical medicine that deals with clients seeking health care because of serious health problems or potentially hereditary disorders. They look for information on the diagnosis, recurrence risk, prognosis, possibilities for treatment and reproductive options. Individuals or families with specific problems are referred to clinical geneticists for consultation. Traditionally, the main focus has been on chromosomal anomalies and monogenetic disorders with Mendelian inheritance patterns. Public health genomics differs from clinical genetics by its focus on populations rather than individuals or families. Moreover, its focus is on genomics rather than genetics. This

might imply an emphasis on common and multifactorial disorders as well as – with regard to ELSI issues – a shift from individualist ethics to social ethics and its guiding principles.

b) PHG versus community genetics

The benefit of the individual is central in clinical genetics, but also in community genetics. But while clinical genetics deals with inviduals and families that have been identified, community genetics aims at locating people within the wider community who may be at increased genetic risk, but have not yet been identified (ten Kate et al 2010).

This is how community genetics is defined in the *Journal of Community Genetics*:
"Community genetics is the art and science of the responsible and realistic application of health and disease-related genetics and genomics knowledge and technologies in human populations and communities to the benefit of individuals therein. Community genetics is multi-, inter- and transdisciplinary and aims to maximize benefits while minimizing the risk of harm, respecting the autonomy of individuals and ensuring equity" (ten Kate et al 2010).

PHG and community genetics are similar in many respects, but differ, for example, in their principal aim. While the former aims at public health, e.g. at increasing the health of the population, the latter aims at the benefit of the individual (ten Kate 2008). It is a matter of dispute whether the differences between PHG and community genetics are merely a question of emphasis or are more fundamental. With regard to ethical evaluation of PHG, it is important to analyze whether principles of social ethics are given priority over those of individualist ethics or, more in general, whether and how both ethical perspectives are balanced.

c) PHG versus traditional public health

The main difference between public health and public health genomics is that the former has focused almost exclusively on environmental or social determinants of health and disease and paid almost no attention to genomic variations within the population. The goal of public health genomics is (1) to understand both the genetic and the environmental/social factors contributing to disease and how these factors interact (there are no pure 'genetic health problems'), and (2) to propose preventive measures directed at susceptible individuals, families and populational subgroups based on their genomic risk profiles (Brand 2005; Brand et al 2008). According to Brand, "Public health in the future will be quite different from public health in the past and will go personalized" (Brand 2011).

In such a model, health services will be tailored to the genetic makeup of each patient. But by directing preventive measures towards suceptible individuals and groups, PHG faces the challenge of balancing a population approach with an individual approach (see Rose above). According to Cleeren et al these approaches should be seen as complementary rather than mutually exclusive (Cleeren et al 2011). In contrast to this, some protagonists of PHG postulated that a new paradigm for public health genomic intervention should be developed which "must be informed by issues beyond the legal and ethical parameters of autonomy and privacy". (Knoppers 2005) Emphasis should be shifted from the principles of individualist ethics (such as autonomy, informed consent, or privacy) towards the ethical principles of reciprocity, mutuality, solidarity, citizenry and universality. (Knoppers and Chadwick 2005).

A middle road, however, would be a stratified approach that focuses on certain characteristics, such as age, sex, or genetic variants, and by means of these identifies subgroups or strata of patients who are more or less likely to respond in a particular way to a treatment. This approach can be viewed as a synthesis of the individual and the population approach (Burton et al 2013). It is not yet clear, however, how such synthesis could be achieved with regard to the (at least partially) conflicting ethical principles of individual and social ethics.

PHG focuses on genes and genomes rather than on identifying disease-causing factors in social or natural environments; hence there seems to be a prefence for identifying persons at risk and for individualizing responsibily for health. Since biological classifications have always served as a matrix for social stratification, ELSI analysts and policy makers need to be aware of possible processes of social stigmatization and discrimination which may develop in the slipstream of genetic stratification and take proactive measures to prevent them. Prioritisation of resources, for research and for clinical applications, is also an ethical issue and policy-makers must take account of the extent to which improvements in population health are likely to be delivered by PHG and/or alternative approaches, as well as possible harms to the individual.

d) Implications of public health organization for the implementation of genomics

Public health may be organised in different ways. In Europe, there are two prototypical models (and some intermediate ones). One is the tax-based system (for example in the UK), the other the insurance-based system (for example in Germany). In tax-based health care, the coverage of health services, including public health, is extended across the population as a whole. In insurance-based systems, health services are initially aimed at those who are 'members' of the social insurance system. While in the UK public health services are governed nationally and delivered by state institutions, in Germany they are governed regionally and delivered by private physicians. The Netherlands is an intermediary case with an insurance-based system, but with highly centralised and partially tax-financed public health arrangements (Aarden et al 2011).

A recent study indicated that the way genetic technologies were applied to identify people with familial hypercholesterolaenemia were influenced by differences in health care systems. The different health care systems of UK, Germany and the Netherlands led to different patterns of exclusion and inclusion. The conclusion was that public health genomics gets constituted differently in different countries due to differences in health care systems (Aarden et al 2011). With regard to the European perspective it needs to be ensured by future policies that the possible benefits (and riks) of the implementation of genomics in the public health care systems are not unequally distributed.

To sum up the conclusions which can be drawn from this comparison: PHG differs from related fields in that it focuses on populations rather than on individuals or families, on genomics rather than genetics, on common and multifactorial disorders rather than on rare, monogenic diseases, and on the guiding principles of social ethics rather than on those of individual ethics. Although several scholars have discussed this issue, it is not clear yet, how both sets of ethical principles can be balanced in a 'middle road' or synthesis. Since PHG aims at identifying persons at risk, policy makers need to be aware of the potential for social stigmatization and discrimination of such an approach and hence proactive measures need to be taken in order to prevent such development. Furthermore, it has to be made sure that investments made in order to improve population health do not result in unethical neglience of the health of individuals or small groups. Finally, it needs to be ensured that – despite evidence of the considerable differences in health care systems – the possible benefits of genetics and genomics will be evenly distributed to all european citizens.

2.3 Genomics in different fields of practice

This discusses how the more general reflections of the preceding sections become relevant for specific application of genomics in more detail. For this reason we are first going to describe three fields of practice which up to now have primarily been guided by individualist ethical principles, but where the application of genomics in a public health perspective raises ethical issues in a new or modified way.

a) Individual whole genome analysis

Until recently, most clinical genetic testing was initiated by specific questions and directed either to karyotype analysis or structural analysis of one or a small number of genes suspected to be involvend in the development of a disease. With increasing technical efficiency and sophistication, individual whole exome or whole genome analysis (WGA) becomes more and more affordable, at least in some health care systems. To date, WGA has not only been rapidly integrated into clinical research, but is currently marketed to health-care practitioners and consumers alike.

In principle, WGA can be applied to different fields relevant for public health. For example, the comprehensive detection of carrier status of allels for recessive genetic diseases like cystic fibrosis or thalassemia; identification of specific genetic components in common diseases; genetic profiling of newborns, or detailed tumour characterization in oncology. In essence, WGA might be applied in different settings (diagnosis in patients with symptoms, research, pharmacogenomics, presymptomatic testing and population screening programs) each of which raise different questions (van El et al 2013).

Compared to other more limited or directed analyses, WGA is expected to have an increased potential to identify the genetic components of health problems. It is also hoped that it may be even less expensive than current techniques in the future (Heger 2011). Whereas some findings will turn out to be clinically important and actionable, most of the data generated may not be related to the initial diagnostic question (van El et al 2013). The volume of sequencing data generated for a single individual and the wide range of findings from whole-genome sequencing raise critical questions about the return of results and their potential value for end-users (Facio et al 2013). Apart from this, ELSI-related questions range from whether a truly infomed consent to such a comprehensive analysis is possible at all due to the harm which could be induced by receiving unsolicited findings or getting to know genetic alterations which could negatively impact on health without preventive measures being available. Other issues concern the right of parents to make far reaching decisions about full genome analysis for minors without knowing the possible benefit of such an analysis at the time taken, as well as privacy protection and acccess rights. “Many of the issues related to WGS [WGA] are not entirely new, but the scale of the challenge certainly is.” (van El et al 2013)

The question therefore is whether such testing should be implemented in routine clinical practice and if yes, how and under which circumstances should it be done? There are at least two main options to deal with these challenges:

- The first 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. Although this option may look the most ‘simple’ or ‘rational’ from the technical point of view, it clearly is in conflict with established ethical principles. For example, informed consent of the analysed individual cannot be achieved and it is doubtful whether parents are entitled to allow such an analysis if there is no immediate clinical benefit. Another problem is that the massive amount of data produced create a tremendous threat to privacy and confidentiality. Last not least, although sequencing and individual GWA could become less and less costly, the infrastructure needed for storing, securing and administrating individual genomic data will create a long lasting burden for the public health care system without knowing whether the data may ever be of use for the individuals analyzed or whether they create a return for public health.
- Another option is to use whole genome sequencing only for specific purposes and when it is indicated that the individual patient may benefit. This option is suggested by the PHG Foundation. It recommends that: “Next-generation sequencing technology should be implemented (for example within the UK NHS) in the short to medium term for applications where it offers clear clinical or cost benefits over existing tests – specifically, for the diagnosis of diseases with a strong heritable component and the management of cancer” (Wright et al

2011). Furthermore, the Public and Professional Policy Committee of the European Society for Human Genetics (ESHG) recommended (*inter alia*) that, "It is preferable to use a targeted approach first in order to avoid unsolicited findings or findings that cannot be interpreted. Filtering should limit the analysis to specific (sets of) genes. Known genetic variants with limited or no clinical utility should be filtered out (if possible neither analyzed nor reported)." (van El et al 2013).

Our group would rather support the second option. It restricts the amount of generated data as much as possible to what is clinically valuable; avoids as far as possible the production of unsolicited findings; limits problems associated with privacy and access; and eases the burden of information and consent for patients and doctors involved in such analyses.

b) New screening programs

Another challenge which comes along with the growing capacities of high throughput technologies for genome sequencing and the falling costs for it, is the feasibility of genetic and genomic screening on a population level. Although genetic screenings have been performed for quite some time on whole populations (Cousens et al 2010) or specific groups (Scott et al 2010), such screenings were in most cases directed to one or a limited number of genes, chromosomes, or gene products. With the advent of genomic technologies, the whole exome or genome becomes a potential target of such screenings.

Compared to genetic testing, which is directed at persons with an indication, usually consisting of a family history of a disease, in genetic screening a test is not offered to persons known to carry an increased genetic risk, but to every member of a population or a specific group "without symptoms or other indications that would make such testing clinically necessary". (van El et al 2013) Furthermore, in genetic testing the request is usually initiated by the patient who is interested in learning about his or her personal risk, whereas in screening the test is offered by the health care institutions to everybody in order to prevent diseases for the benefit of the individual and/or public health.

Genomic technologies accelerate the possiblities of genetic screening with regard to quantity and quality. There are different fields where genetic screening could be performed. An important one is reproductive medicine.

- *Newborn screenings* are the best known screening programs and well established in many different countries. They are performed just after birth in order to identify (genetic) disorders that can (and should) be treated early in life in order to prevent future disease or disability. The tests are done on a small blood sample obtained by pricking the baby's heel with a lancet. The test battery includes treatable or preventable diseases and is restricted to them. The most common condition in newborn screening programs is congenital hypothyroidism, which is usually not a genetic condition. Apart from this disorder only a limited number of genes and/or their products are searched for or detected. Some authors anticipate the introduction of genomic technologies or a 'genetic profiling of newborns' by microarrays or WGA in newborn screening. Also, in whole genome sequencing and analysis the restriction could be made to gene variants with clinical utility. However, the technology allows the analysis to involve many treatable as well as untreatable disorders. Many genetic markers might be revealed which are most likely of no clinical use at the time of detection and possibly throughout the lifetime of the individual if no filtering was applied.
- The same would be true if genomic technologies were introduced as an instrument of *prenatal screening.* A first step in this direction is the implementation of *non invasive prenatal testing (NIPT)* by commercial companies in some European and US-American markets. Other than amniocentesis, which is an invasive procedure based on fetal DNA from amniotic fluid with a slightly increased probability of stillbirth, NIPD can be performed on

fetal DNA from maternal blood. NIPT is currently used primarily to detect trisomy 21 (Down Syndrome), but further development is on its way which will allow the detection of additional anomalies of the karyotype and most likely alterations on the level of the DNA. New strategies and procedures for noninvasive whole fetal genome recovery are currently being developed (Chen, Wang et al 2013). The advantages of NIPT for chromosome anomalies could outweigh the disadvantages (less invasive tests, more valid results). The potential application to identify many more disorders needs debate. Will informed decision making in the context of pregnacy be possible if the test is to identify multiple disorders? Will couples understand the results? It would also accelerate the ethical problems already connected to prenatal diagnosis and screening and the choices which have to be made in this context.

- *Preimplantation genetic diagnosis (PGD) and preimplantation genetic screening (PGS)* are other procedures where advanced genomic technologies may be applied. It is envisioned that they may allow to sequence the DNA of individual cells for embryo diagnosis. Such technologies should provide the opportunity to simultaneously analyze single-gene disorders and perform an extensive comprehensive chromosome screening/diagnosis by concurrently sequencing, counting, and accurately assembling millions of DNA reads (Martín et al 2013). The growing amount of information available on the embryos may be helpful in embryo selection on the one hand; on the other hand it may also create new or accelerated ethical problems for the prospective parents since it does not automatically coincide with an increasing understanding of the prospects of an embryo.
- Furthermore, comprehensive embryo testing may coincide with prior *preconception carrier screening.* According to Hens et al: "The increasing complexity and amount of information yielded by comprehensive testing techniques will lead to challenges to the principle of reproductive autonomy and the right of the child to an open future, and may imply a possible larger responsibility of the clinician towards the welfare of the future child. Combinations of preconception carrier testing and embryo testing may solve some of these ethical questions but could introduce others." This creates a need for a thorough rethinking of traditional ethical paradigms regarding medically assisted reproduction (Hens et al 2013).

One of the core ethical questions in this context is whether genomic data eases the burden of decision making in the context of reproduction or, on the contrary, makes it more complex. Most likely, the latter will be the case due to the tremendous amount of information which needs to be taken into consideration and weighted. Another issue pertinent to genetic screening in the field of reproduction is eugenics. It is generally agreed that public health genomics should not have the goal of 'improving the gene pool', as suggested by eugenicists during the early twentieth century. Hence, it should not include genetic screening programs aiming at genotypic prevention, i.e. reduction of the incidence of certain genotypes (Juengst 1995). Decisions to undergo prenatal screening and to terminate pregnancies based on the results of genetic testing should be strictly personal (Biesecker 2001) and never be influenced by the public health goal to reduce the incidence of the burden of disease.

The application of genetic and genomic technologies on a large scale in order to prevent diseases might nevertheless be conceived as a modern version of eugenics. Most proponents and clinical users of such technologies regard such a conception as misconception, because amelioration of the gene pool is not regarded as a goal of public health. Certainly old-style eugenic ideology and abuses are something of the past. Nevertheless, "The potential of abuse of any technology is largely dependend on the social context within which that technology is used". (Proctor 1992: 84) The danger, therefore, is not that someone will try to improve the gene pool of the population (if that would be possible at all), but that with the introduction of powerful genomic technologies, there may be societal expectation and perphaps an increase in pressure to avoid the birth of children with genetic diseases or syndromes.

Furthermore, the widespread application of reproductive genetic testing may dramatically reduce the frequency of livebirths with genetic syndromes like Down Syndrome – and individuals potentially affected by it (Cole and Jones 2013). Such an effect may be regarded as desirable by public health and by the families affected by such conditions. It may even be guided by the best intentions of all parties involved. However, although parental and clinical decisions are not determined by coercion but by deliberate and by informed consent, they inevitably contain value judgements about children with genetic diseases or syndromes and hence may be perceived by those living with such a conditions as humiliating and discriminatory and regarded as some form of 'private' eugenics (Scully 2008).

In view of these considerations geneticists "Should recognize that their research may have implications for those with disabilities; they should recognize the impact of the historical trauma of the eugenics movement, and seek to involve people with disabilities in discussions about policies that affect them. Dialogue can be messy and uncomfortable, but it is the only way to avoid the mistakes of the past and to ensure a more equitable, and healthful, future." (Miller and Levine 2013) Policy makers should be reminded that – no matter how desirable it might be to reduce the incidence of genetic diseases (whether for the sake of the individual, the family or the community), it must never be pursued by applying any sort of direct or indirect pressure, be it legal, social or economical. That this is not a mere theoretical possibility was shown by a recent analysis of policies followed to implement genetic screenings. It concluded that such policies "Have often been determined by technological capability, advocacy, and medical opinion rather than through a rigorous evidence-based review process", and that ethical principles and opportunity costs often have not been taken sufficiently into account (Grosse et al 2010). A thorough review with regard to the ethical and social implications is therefore – besides the demonstration of clinical utility – one of the most important preconditions when considering the implementation of genetic or genomic screenings.

c) Direct to consumer testing

Direct to consumer testing (DTCT) is also a field where massive new ethical, legal and societal challenges emerge. It is characterized by the fact that companies advertise and sell genetic tests and analyses outside the health care system. Available tests range from preconseptional carrier testing for single gene disorders and genetic association tests for predispositions, through to complex, multifactorial diseases. Furthermore, various companies request, directly or indirectly, healthy individuals to provide medical and/or health information as well as samples of body fluid or cell samples in order to extract genetic information. This development creates an number of ethical and societal concerns, which will be discussed in detail in Section 5.

2.4 The need for proactive policy

Provided the number of examples increases and genomic technologies as well as the information generated by it become part of everyday clinical practice, disease prevention strategies and public health policy/health care could undergo far-reaching changes. This situation calls not only for reflections on the consequences of this development for the health care system, but also on its ethical, social and legal implications, as well as for exposing existing policy needs.

3 Challenges to existing professional, regulatory and legal frameworks and ethical principles

In the last three decades, great progress has been made in both genetic and genomic research. In a recent report, the European Society of Human Genetics described how current developments are *changing the landscape* in which genetic testing is being provided (Hastings et al 2012). Without aiming to provide a comprehensive analysis of all relevant ethical and social concerns, we aim to describe in this section some of the challenges that are inherently linked to the introduction of genome-based applications in health care and public health. This includes applications related to single-gene disorders and common complex disorders, and applies to diagnostics, as well as to preconceptional, prenatal or postnatal screening as well as stratified interventions. In this short overview we aim to describe current challenges to ethical principles like informed consent, the right not to know, privacy, equity, as well as for the conception of medical responsibilities, the fields of insurance, employment and population screening.

3.1 Challenging informed consent

The unethical use of subjects in research has led in the second half of the 20th century to the development of principles for medical research involving human subjects, such as The Nuremberg Code and the Declaration of Helsinki. In this context, informed consent has been developed as a basic principle in research ethics. The attention to the rights of research participants has gradually increased and also the attention to informed consent as a right for patients in the context of medical care. Informed consent can be specified as concept entailing an information component and a consent component (Beauchamp and Childress 2001). The information component refers to disclosure of information about the purpose, implications, or risks of an intervention, or its alternatives. Information should be provided in a way that is adequate to at the level of understanding of the recipient of the information. The consent component refers to both a voluntary decision and an authorization to proceed.

For healthcare situations, many countries have enacted patients' rights legislation. Also most medical associations have emphasized in their professional guidelines the importance of informed consent in medical interventions. At the European level, the Convention of Human Rights and Biomedicine has stipulated that: ''An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it.'' For healthcare professionals the obligation to obtain consent for a medical intervention is associated with the duty to provide appropriate information about the purpose and nature of the intervention as well as the consequences and risks. The same *convention* also advances that predictive genetic testing should be subject to appropriate genetic counseling.

In practice, however, in the light of the changing landscape in human genetics, actual debates revolve around the implementation of this important principle. When thinking about the implementation of whole genome sequencing, the huge amount of sequencing data that becomes available is in contrast with the capabilities and possibilities of interpretation of this data. Debates exist about how much information should be provided to individuals before undergoing such a test, which results should be disclosed to the patients (and that might also be relevant for their relatives) and to what extent the patients should be able to decide for themselves the amount and the type of information that should be reported back (Ostrer 2011; Thorogood et al 2012; Berg et al 2011). As information is not only relevant for the individuals undergoing this test, but also for family members, more questions are being raised about the importance of involving or informing family members. Various conflicting values and practical concerns are mentioned in these debates, including the autonomy, beneficence, non-maleficence, right to access information, interpretation cost, counseling costs, and utility of these findings (Rigter et al 2013).

3.2 Challenging the right not to know

The 'right not to know' has been recognized in various jurisdictions as the right of individuals to instruct their health care professionals against the disclosure of certain health information. Especially in the context of genetic testing, this right has been recognized as a respect for individuals' wishes not to be informed about specific genetic information or not to be tested for a specific genetic condition. The right was stipulated in the UNESCO Universal Declaration on the Human Genome and Human Rights: "The right of every individual to decide whether or not to be informed of the results of genetic examination and the resulting consequences should be respected" (UNESCO 1997). It is also stipulated in the European Convention on Human Rights and Biomedicine: "Everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be so informed shall be observed."

The respect for autonomy is often defended as the theoretical underpinning for the 'right not to know' (Andorno 2004). It acknowledges that patients are in the position to decide which information they want or don't want to receive. This has been considered particularly relevant in the context of minors. Minors might not have the necessary maturity to take health decisions now, but in the context of health information that might only affect minors when they are adults, there is no urgency and necessity to process this information now. Although a child may not have the necessary competence and maturity to take autonomous decisions now, there are important reasons to keep certain future options open and not limit them by current decisions that do not need to be made now. A typical example of genetic testing to which the 'right not to know' is usually applied, is predictive genetic testing for a late-onset disorder such as Huntington's disease. The knowledge of the absence or presence of a mutation gives certainty about the development of the disorder later in life, but there is no possibility to alter the prognosis. The absence of medical benefit and the absence of any medical urgency provide no compelling reason to test minors under those circumstances, and usually guidelines suggest delaying testing until minors can decide for themselves about undergoing this test.

However, various developments might challenge this 'right not to know'. For an increasing number of conditions, treatment or prevention will be possible if a diagnosis is made early, for instance in metabolic diseases (heelprick screening), oncogenetics and cardiogenetics. Thus, in such cases, the 'duty to inform' would have to be balanced against the 'right not to know'. Furthermore, looking at the entire genome will reveal 'incidental' findings, which are unrelated to the clinical request, as well as a number of genetic variants for which the meaning remains unclear. In their recent document, the ACMG challenges existing clinical standards for genetic testing in children: "The ethical concerns about providing children with genetic risk information about adult-onset diseases were outweighed by the potential benefit to the future health of the child and the child's parents of discovering an incidental finding where intervention might be possible." In their conclusions about the communication of incidental findings, they therefore reported that those should not be limited by the age of the person being sequenced. There is broad consensus that medical benefit, whereby a genetic test is likely to provide useful information for the medical management of the child, the test is either permissible or even obligatory (Borry et al 2008). 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. This new situation challenges and intensifies debates about clinical utility, policies regarding return of results and procedures with regard to informed consent (Hastings et al 2012; Biesecker et al 2012).

Although controversial, some experts (Goldenberg and Sharp 2012; Tarini and Goldenberg 2012) believe that once *next generation* sequencing technologies are sufficiently robust and affordable, all newborns will have their genomes sequenced at birth replacing in this way the current newborn

screening and replacing additional genetic tests that might be necessary later in life. Disagreements over the value of genomic profiling of newborns have centered on the pace of technological development, delivery of clinical value, major ethical, legal and social implications such as safeguarding the autonomy of the future adult, and issues around data storage and access (Wright et al 2011). Dealing with such a huge mass of sequence data is a new challenge inside and outside the clinical setting, and provides a new set of questions for society, related to the rights of parents to access the genetic information of their children, the best interest of the children, the right to know and not to know, privacy rights, the clinical utility of retrieved information, the level of consent, the 'duty to recontact' of healthcare professionals, and counselling issues. The debate on the expansion of newborn screening is confronted with a discussion on expanded interpretations of the 'benefits' of NBS: from what is good for the infant to what might be potentially good for the infant, to what might be good for the family (i.e. reproductive benefit) or to what might be good for society at large (i.e. for research) (Bombard et al 2010).

With the development of direct to consumer (DTC) genetic testing companies (cf. Section 5), much debate has been developed around the acceptability of testing minors within the realm of DTC genetic testing. Several studies suggested that particular types of parents might have an interest in predictive genomic testing in their children (Tercyak et al 2011, Su et al 2011). Nevertheless, next to concerns related to the impact of such testing, there are also concerns about the fundamental rights of minors (Human Genetics Commission 2005), since this practice is largely incongruent with current standards concerning genetic testing of minors. It questions whether professional standards should change in this domain, or whether legal safeguards should be put in place to in order to address the raised concerns.

3.3 Moving professional responsibilities

In view of the increasing availability of genetic information, it is important to clearly identify the responsibilities of professionals. In some cases, individuals might not confer known relevant genetic risk information to family members. Various reasons might explain this behavior, such as the desire not to cause anxiety or alarm, living remotely, familial conflicts, absence of any contacts, adoption, generational gaps or complex family relations (Clarke et al 2005). In other cases (e.g. in the case of children) relevant information might just not have been communicated. In such cases, legal concerns have been raised about the obligations of physicians to respect (genetic) privacy on the one hand and the potential legal liability from a failure to notify individuals on the other (Borry and Dierickx 2008). It questions to what extent physicians have in this context a duty to warn. In light of the technological developments, healthcare professionals might also be confronted with an increasing amount of information. For example, variants of unknown significance might suddenly turn out to be deleterious variants. This questions to what extent healthcare professionals should 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 recontacted? Is it even logistically possible to put such a responsibility on healthcare institutions?

The implementation of whole genome sequencing has also created the question 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 (American College of Medical Genetics 2013). This is currently part of an intense debate, in which some hold the position that incidental findings should not be reported until there is strong evidence of benefit, while others have argued that even in the absence of evidence it should be possible to establish a list of disorders for which preventative measures and/or treatment are available.

3.4 Challenging privacy

The right to privacy is recognized at the international level in various binding and non-binding legal documents. With respect to privacy in the context of genetic data, UNESCO adopted the Universal Declaration on the Human Genome and Human Rights in 1997. This document states that: “Genetic data associated with an identifiable person and stored or processed for the purposes of research or any other purpose must be held confidential in the conditions set by law.” At the European level, the privacy of individuals and the protection of personal data is addressed under Article 8 of The Charter of Fundamental Rights of the European Union: “Everyone has the right to the protection of personal data concerning him or her.” The notion of privacy is also integrated in the European Convention of Human Rights and Biomedicine and its additional protocol on genetic testing. See for example article 16 of the last document: “Everyone has the right to respect for his or her private life, in particular to protection of his or her personal data derived from a genetic test.” A European Directive (which is currently undergoing a process of adaptation) controls the processing of personal data.

Logically, related to the predictive nature of the results in the context of genetic testing and the processing of genetic information, a lot of attention has been given to the protection of confidentiality and privacy, including the elaboration of appropriate security measures to protect and control access to personal information. In the context of our healthcare systems, the development of electronic health records has led to increasing attention on how the advantages of the electronic collection, analysis and exchange of patient files could be combined with a high level of data protection.

A few challenges are touching debates on privacy.

Firstly, with the development of whole genome sequencing two types of information that need privacy protection become available: the sequencing data, that is the raw data that needs specialist interpretation, and the analysed data that has been transformed into a lab report. As both types of information relate to the personal data that are being processed, individuals have a right to access this information. At this point a potential conflict might arise, as the access to this personal information might lead to accessing the personal information of a relative. In the context of whole genome sequencing this issue is crucial, as a further analysis of the sequence data might have familial consequences (Matthijs et al 2013).

Secondly, in view of the increasing amount of whole genome sequencing data being generated, a balance has to be found between sufficiently protecting privacy on the one hand, and on the other, the possibility of using this information for improving patient care and further research. At the level of research, an important emphasis has been put on making data and research results available to other researchers. Therefore databases have been elaborated that require researchers to deposit data used for their publications in order to enable to use those for further research. In endeavoring to balance respect for privacy and enabling research, debates have been focused on the limits of anonymization or de-identification, and the elaboration of data sharing policies.

New studies also show how it becomes more and more possible to identify individuals from non-identifiable information. In 2008, Homer et al (2008) showed how individuals could be identified in large datasets. Recently, Gymrek et al (2013) have shown how: “The full identities of personal genomes can be exposed via surname inference from recreational genetic genealogy databases followed by Internet searches.” It is clear that sharing of research data will make it easier to identify individuals by linking together various sources of information, including genomic information, medical information or data sets. This creates concerns about potential third parties accessing those data sets, including the police, employers or other institutions.

Even if healthcare and research infrastructures build robust strategies to protect privacy to a maximum, new privacy risks are developing by the increasing availability of DNA ancestry and genealogical tests (Borry et al. 2013). By using those tests, cases have been reported in which individuals incidentally found out non-paternity events and were able to identify biological relatives that donated gametes under frameworks defending anonymity in gamete donation. This type of information has a huge impact on issues related to the disclosure of donor conception to donor-conceived offspring, the anonymity debate and the provision of non-identifying information to donor-conceived offspring. In this regard the difference between non-identifying and identifying information is blurring and information that originally seemed non-identifying might suddenly become identifying. (Borry et al 2013).

3.5 Challenging equity

The implementation of new genetic tests into the healthcare system and public health challenges the provision of genetic testing services in Europe. According to a recent report (Ayme et al 2013), the provision of genetic tests is organized differently in various European countries, with clear differences in the number of laboratories, in the balance of private and public laboratories, in the number of laboratories accredited and/or participating to External Quality Assessment Schemes, and in the funding process (i.e. with some countries functioning on a fee per test, while others function with a global budget). This might create situations that prevent equitable access to tests across Europe.

In light of the proliferation of genetic tests, it will become more and more important to support the development of the clinical utility of tests as part of the care pathway (see Section 6). In order to keep a viable healthcare system and the appropriate use of limited healthcare resources, it is crucial to allocate resources to genetic tests that have clinical utility. Despite decreasing laboratory costs per test, the increasing cost of interpretation, patient counseling and follow-up care, and the increasing referral for testing might otherwise hinder accessibility to genetic testing. Although many have referred to the increased accessibility of sequencing due to its decreasing price, the downstream costs of this test might largely outweigh the cost of the sequencing, due to the large amount of information generated and the cost of analysis, the cost of counseling, the cost of false positives and negatives (and their medical consequences), etc. Therefore, it will be important that those tests that are most beneficial to patients are becoming available to them based on an appropriate evaluation of their clinical utility, and not only on the basis of technological availability.

3.6 Challenging debates on insurance and employment

The issue of the use of genetics in private insurance and employment has been the thrust of ongoing debate in the public realm, expert panels, and parliaments throughout Europe. In the last decade, the most prominent governance strategy to deal with the issue has been the enactment of genetics-specific regulations in some countries, prohibiting 'genetic discrimination' in insurance and employment in some circumstances. These regulations emphasize genetic information as distinct from other medical information and try to prioritize interests in genetic information. The increased availability of genome-based information through whole genome sequencing questions the way insurers and employers might look at genetic information and whether elaborated legislative and policy options with regard to access to genetic information should be reconsidered. An issue being raised is the question concerning the existing gap between fears of genetic discrimination and actual discrimination. Moreover, critics have argued that focusing on genetic risks might result in the relative underprotection of non-genetic risks, like lifestyle risks. In this regard, it is important to mention the public consultation of the Council of Europe regarding the use of predictive health-related data, in particular genetic data, in the field of insurance. This activity took place within the

aim of developing a legal framework for the protection of human rights with regard to the use of genetic testing in the medical as well as non-medical field.

3.7 Challenges to population screening

Next to implementation into the diagnostic setting, considering to what extent genome-based interventions and technologies can be used for screening purposes raises important questions. Based on the idea of early detection and potential prevention, enthusiasm for screening is usually high. Nevertheless, harms related to screening do exist. In particular, in relation to the anxiety about the results, negligence of residual risks, false positives and false negatives, potential (unnecessary) follow-up tests and treatments, potential over-diagnosis and so forth (Woolf and Harris 2012). Therefore, it is important that there are clear guidelines in order to ensure a responsible introduction of genome-based interventions in public health. Various models and frameworks for translation from research to practice in genomics have already been developed (see for elaboration Howard et al 2013). A careful translation process should be balanced in order to avoid a 'premature translation' (Burke et al 2012). Relevant criteria include the importance of a reliable and valid test instrument and a qualitative 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 (Howard et al. 2013). The utilization of these principles as a guiding framework of tests should have priority over the reference to 'personal utility.'

While some seem to assume that information about genetic susceptibility to disease might change individuals' health behaviour, the reality is that there is hardly any evidence that this might actually change long-term lifestyle. If any population-based risk-stratification is likely to be implemented in public health, it will need to be shown that it is efficacious and cost-effective to screen for that disorder (Hall et al. 2010).

4 Data travelling between research and healthcare

4.1 Biobanks and Big Data

Translation of genetic and genomic tests for complex diseases into clinical practice requires large-scale databases because individual genetic variants have only small effects on risk. The concept of providing personalized risk assessments for common diseases, based on SNPs or whole genome sequences, perhaps combined with non-genetic risk factors, depends on integrating electronic medical records and genomic data, perhaps for whole populations. It implies: (i) that data collected for medical purposes, as part of the individual doctor-patient relationship, will be shared for research purposes and statistical analysis; and (ii) that interpretations of this data will later be fed back to individuals, within traditional health services, or perhaps outside them as commercial services (including direct-to-consumer services). This requires significant transfers of raw data and interpretations of this data from patients to researchers and back to patients. Policies are needed in relation to the collection, storage, sharing and interpretation of this data and the biological samples from which genomic information is derived.

Databases of stored health information linked to biological samples are known as biobanks and statistical analysis of large databases is increasingly being known by the name Big Data.
Some experts argue for a gradual expansion of existing genetic services by including new genetic and pharmacogenetic tests in health services as and when they become available. In this approach, new tests would be implemented widely only when their clinical validity and utility has been demonstrated. Under this scenario, the use of new technologies such as whole genome sequencing (WGS) would be restricted to research and (at least initially) introducing the more promising and well-developed clinical applications, such as diagnosing rare unexplained symptoms of genetic disorders in young children (Section 6). Research results and clinical applications would be clearly separated and introduction of new tests would be based on technology assessment and the informed consent of the individual patient.

However, this principle of separation between research and clinical care is challenged by the concept of Public Health Genomics, especially proposals for the whole population to have their whole genome sequenced, perhaps at birth. This idea involves the transformation of health services, to create new systems, which revolve around information stored in electronic medical records, with the addition of genotypes or whole genomes. Under this scenario, patients would receive a personalised risk assessment based on the information stored about them and this would form the basis of their future care.

This approach involves:

- A significant increase in the amount of personal information collected and stored about every individual (including babies and children);
- Sharing of personal data and genomes with large numbers of researchers, probably involving some form of public-private partnership, with access to stored data by multiple third parties, including overseas;
- Major up-front investment in transforming infrastructure in the absence of evidence of significant health benefit for common diseases (see Section 5);
- A shift away from hypothesis-driven science to data-driven science (data-mining);
- A blurring of the line between research and clinical application, as interpretations of much of the stored data may be preliminary and uncertain;
- An obscuring of the role of the treating physician and his or her responsibilities for the patient, in contrast to those as a researcher (or as a provider of data to the research system);

- A significant shift in resources away from people who are sick (i.e. present with symptoms) towards people who are healthy (based on their personalized risk assessments);
- Major changes in the roles of individuals, families, medical professionals and commercial companies in medicine, involving increased use of computer algorithms, decision-support systems and online services in the diagnosis and prediction of disease.

Enthusiasts of Big Data in healthcare see the main objective as identifying correlations between genotype and phenotype (the physical characteristics of a person) (Chen, Qian et al 2013). The use of large data sets and sophisticated statistical techniques increases the statistical power to detect weak correlations such as those between genetic variants such as SNPs and common, complex diseases. However, predictions based on multiple correlations can have low predictive value and/or clinical utility and be misleading for a variety of reasons, particularly when the effect size of each SNP is expected to be small. Some statisticians have therefore questioned the value of Big Data as a means to do research (Ioannidis 2013), whilst researchers from other disciplines such as evolutionary theory and psychiatry have highlighted the difficulties in making sense of all the information (Buchanan et al 2009; Mewes 2013).

Like all science, Big Data or 'hypothesis free' science is based on hidden assumptions that define a paradigm: for example, an emphasis on using biological data (particularly genomic data) to predict individual risks, rather than environmental or social data (although the latter may be integrated at some stage in the future); the treatment of genetic variants such as SNPs as fixed risk factors, rather than context-dependent ones; an assumption that identification of future genetic variants will increase the utility of personalized risk assessments sufficiently for their use to improve health outcomes; and a focus on individuals and individual actions (lifestyle changes or medical interventions) rather than population-level policy responses to improve public health (such as stricter regulation of medicines to prevent adverse drug reactions; or measures to restrict marketing of unhealthy foods) (Pearce 1996).

Whilst some argue that a shift to Big Data and the associated transformation of health services is inevitable, in reality the pros and cons of alternative scenarios to expanding the use of genomics in healthcare involve policy decisions about a variety of issues. These include decisions about infrastructure and investments, as well as what regulations and safeguards would need to be in place for research participants and patients.

4.2 Implications for consent, privacy and patient rights

The most obvious concerns about Big Data relate to privacy and consent to the use and storage of vast quantities of personal information. These issues are exacerbated by the role played by whole genomes or large panels of SNPs as biometrics, which can be used to track and identify individuals and their relatives (including non-paternity).

Large-scale biobanks, which link medical records, biological samples, and other data, pose challenges to traditional informed consent because data may be shared with large numbers of researchers, including commercial companies, both nationally and internationally, for purposes which may be unclear when the data sets are collected. Legislation that rules this type of data exchange across national borders is not in place. Considerable differences with regard to implementation and enforcement of legal provisions exist (Forgó et al 2010) even among the countries of the European Union which have signed the data protection directive (Directive 95/46/EC). Data protection rules are currently being revised by the new Data Protection Regulation and are likely to form part of the new US-EU Free Trade Agreement.

The principle of informed consent (see Section 3.1) is tightly connected to the physician-patient-relationship; by respecting it the physician acknowledges the patient's autonomy, protecting the patient's rights and also protecting the physician against accusations and litigation (Kollek 2009; Wolpe 1998). Quality information and voluntary consent are precautions against unwanted and unwarranted interventions and informed consent therefore ensures that patients or research participants are neither deceived nor coerced (O'Neill 2003). If the well-being of the patient is at the foremost interest of the physician, informed consent must be an indispensable part of this relationship.

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 (Wallace 2005; Levitt 2005; Godard et al 2004). The concept of Big Data and open sharing of data with a variety of public and private institutions makes it difficult for physicians to reliably inform their patients about how their data might be used and to provide guarantees about confidentiality. In many cases it is unclear whether or how the public have a say in deciding what is in the public good. The concept of 'presumed' consent differs from broad consent and is more controversial: 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. This removes people's choice to take part in some research projects but not others, based on their own views of the risks and benefits.

Proposals to create biobanks of whole populations have led some to argue for large-scale sharing of pseudo-anonymized data without consent (UK Department of Health 2013), allowing data-mining and statistical analysis by multiple institutions and commercial companies, with analysis re-linked later to return results to patients. Pseudo-anonymized medical data and genomes have individual names removed but a unique identifier retained so interpretations of the data can be linked back to the individual later on. There have also been proposals to sequence 'surplus' biological samples or 'excess' blood (collected for tests during medical care or on registration with a healthcare provider) without people's knowledge or consent (Kohane 2011). However, others argue that undermining informed consent is not necessary for medical research and will undermine trust between citizens and researchers (Ioannidis 2013).

Consent for those that lack capacity, and the partially shared nature of genomes within families, adds further difficulties, particularly for children, whose capacity to make decisions about retention and sharing of their data will increase as they grow up (Dowty and Korff 2009). Storage and use of babies' blood spots without consent has proved highly controversial in several countries (Stein 2009; Anderson 2009; The Sunday Times 2010: Greer 2010). Sequencing babies' blood spots, unless the information needed is directly related to their care, removes their right to make their own decisions in the future.

Biobank participants' views may depend on who is given access to their data, with particular concern about the potential for genetic discrimination by insurers or employers (Otlowski et al 2012). The EU's Charter of Fundamental Rights includes a broad non-discrimination clause that encompasses genetic features (37, art. 21). However, legislation varies widely in different member states particularly in relation to the use or potential use of genetic information by insurers. Some studies have also revealed suspicion about the profit motive and other vested interests (including those of patient groups and scientists) and legitimate interests in the way research priorities are chosen (Levitt and Weldon 2005). In future, other issues may arise regarding the sharing of health data overseas, for example with the US and China.

A major current policy debate in the EU is development of the new Data Protection Regulation and the extent to which this should reduce or increase people's individual controls over their health data and electronic medical records. Advocates of Big Data (including many commercial interests) argue that data protection legislation should be weakened to allow data mining of pseudo-anonymized health data and perhaps to exempt such 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 (Schmidt and Callier 2012; Gymrek et al 2013; Nature 2013; Sweeny et al 2013). In fact, it is now widely regarded as misleading to promise privacy protection to research participants in whole genome studies (Clarke et al 2012).

This problem is compounded by the fact that whole genomes or large panels of SNPs act as biometrics or 'genetic fingerprints', linking an individual's biological characteristics permanently to their stored medical records and other data. This allows a form of biological tagging or 'biosurveillance' (Williams and Johnson 2004). The concept of Public Health Genomics implies a role for the government or state in collecting and storing data obtained by medical professionals during the course of patient care. Police and security services access to genetic databases established for health and research purposes have been limited to date because large numbers of genotypes or genomes have not been stored in a searchable form. This is likely to change in future and police access is not prohibited by current legislation (Kaye 2006). Individuals may also be vulnerable to being tracked by others who can infiltrate health service systems or access research data online (such as abusers or criminals seeking to track victims).

Because individuals inherit half their DNA from their mother and half from their father, comparing genotypes or genomes can also identify close relatives and reveal non-paternity. Identification of non-paternity can already occur in some screening programmes for recessive genetic disorders (disorders which require two copies of a mutation to be inherited, one from the mother and one from the father): this must be handled extremely sensitively to avoid negative consequences including family breakdown (NHS). If individuals can be identified from anonymized genomic data it follows that their children can be too and non-paternity could also be revealed outside the professional medical environment.

Concerns about biometric databases run counter to the push for 'presumed' or 'broad' consent to the indefinite storage and widespread sharing of data for research. 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*" (Data Protection Working Party 2012). Valid alternatives must exist for consent to be regarded as freely given (e.g. people must not be forced to seek care elsewhere or go without treatment if they do not want their genomes sequenced). Indefinite storage of whole genomes without fully informed consent also appears inconsistent with the 2008 judgment of the European Court of Human Rights regarding the UK Government retention of innocent people's DNA profiles and fingerprints. The Grand Chamber concluded unanimously that this practice "*constitutes a disproportionate interference with the applicants' right to respect for private life and cannot be regarded as necessary in a democratic society*" (http://hudoc.echr.coe.int/sites/eng/pages/search.aspx?i=001-90051).

4.3 Feedback of interpretations to individual citizens and patients

A further set of issues concerns the nature of the information that is stored and may be fed back to individuals and their families. Because vast amounts of data, and researchers' interpretations of it,

will be retained and data-mined this raises issues about the quality and usefulness of this information to individuals and their families and under what circumstances they should be informed about it (their rights to know and not to know) (see Sections 3.2 and 6). Since the early days of the Human Genome Project, researchers have raised concerns that "*prognostic unknowns and complexities raise the primary ethical implication for the clinical transaction, namely, what constitutes truthful, accurate genetic information for the patient*" (Jonson et al 1996). However, pre-market assessment of clinical validity and clinical utility of many tests is still lacking, at least for commercial services (Section 5). This raises particular issues in the case of children because of the transition of consent and privacy requirements and the rights to know and not to know from parents to child during adolescence. There is much debate about 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 (see Section 3.3). Some ethicists have argued that: "*As long as there is no clear positive balance of advantages and disadvantages, there can be no responsible implementation of whole genome population screening within public healthcare*" (Dondorp and Wert 2013). However, others argue in favour of the individual's 'right to know' and hence be given access to all interpretations of their data. One option is to give people a say about whether or not research findings will be fed back to them in future: however, this approach is complex given the likely uncertain nature of many of the findings and the unsuitability of many tests for screening in the general population (PHG Foundation 2013b). As a result of this uncertainty, different companies may give very different interpretations of a person's risk based on the same DNA (The Sunday Times 2008).

5 Commercial developments

In this section we will discuss various challenges that are currently affecting the field of human genetics that are all linked to certain commercial developments.

Firstly, we have observed in the last five years the emergence of companies that have started to advertise and sell genetic tests outside the healthcare system. The range of direct to consumer (DTC) genetic tests available is broad, from preconceptional carrier tests for single-gene disorders, such as cystic fibrosis (predicting a high risk of having affected offspring if both partners are carriers) to genetic association tests for predisposition, to complex, multifactorial diseases, such as depression and cardiovascular disease. The development of these companies has created concerns with regard to this provision of tests and raised various policy issues. Secondly, various companies have engaged in some initiatives whereby healthy individuals or patients are requested to provide personal medical or health information, as well as a sample in order to extract genomic information. This evolution provides some challenges to the traditional vision on research. Thirdly, we are observing the development of public-private partnerships for data collection, storage and research as well as in the translation towards implementation. This development leads to various ethical concerns. Fourthly, we discuss some developments in the field of patenting and licensing.

5.1 The advertising and/or selling of genetic tests outside the healthcare system

DTC genetic testing is usually defined as the offer and/or marketing of genetic tests directly to the public without the intermediary of a health care professional from the traditional health care system. As has been suggested by the Human Genetics Commission, however, we also include in this discussion 'tests that are commissioned by the consumer' from a commercial company outside the traditional health care system 'but where a medical practitioner or a health professional is involved in the provision of the service.' (Human Genetics Commission 2010). The offer of DTC genetic tests has created various concerns.

Firstly, many concerns have been raised with regard to the limited clinical utility of many of the tests that are being sold. Multifactorial disorders are explained by a complex interaction of multiple genes and environmental factors. All contribute only a modest fraction to the risk of developing a disorder therefore making it extremely difficult to assign an accurate and meaningful degree of risk to each individual factor (Mihaescu et al 2009; Janssens et al 2010; Janssens et al 2011; Mihaescu et al 2011, Palomaki et al 2010). Therefore, many concerns with regard to various DTC genetic tests are based on their limited predictive value. Also in the context of carrier identification of autosomal recessive disorders, concerns with regard to clinical validity may apply. Some homozygotes, because of low penetrance, may never develop overt disease, and/or the expression may be variable (Levenson 2010).

Secondly, DTC genetic testing companies have been criticized for overstating the predictive value and the potential health consequences of the tests they are selling (Caulfield et al 2012). The United States Government Accountability Office concluded that various companies they analyzed were engaged "in some form of fraudulent, deceptive, or otherwise questionable marketing practices" (US Governmental Accountability Office). At the level of information, it is crucial that individuals receive the necessary information about the goal of a test, the decisions that might result from a test (also at the reproductive level), the quality of the test, the potential psychological implications, as well as the meaning of a test for relatives (McQueen 2002). It has been reported that the quality of information on the websites of DTC companies varies and concerns were raised that websites might overstate the quality of the tests in order to increase sales.

Thirdly, the absence of genetic counseling accompanying the provision of test results might be problematic in some cases. Genetic counselling is the process through which information enables individuals to make their own free decisions about testing. In the cases where companies do have health professionals that provide counselling, concerns have been raised as to what extent those professionals are providing independent health advice or are defending the interests of the companies they are connected to.

Fourthly, the fact that consumers can order tests kits through the internet and can submit samples through the mail means that there is no control on the origin of the samples. The risk for non-consensual testing has been reported on various occasions (Greenbaum 2012; Suter 2012; Kamei 2009; Green and Annas 2008). Further concerns focus on the inappropriateness of testing minors if this is not in their best interests. Clinical guidelines focusing on genetic testing in minors have emphasized that the best interest of the child is paramount and that perceived benefits and risks of testing must be carefully weighed when considering a genetic test in minors. Various DTC companies, however, don't follow clinical guidelines with regard to the testing of minors (Borry et al 2009a; Borry et al 2009b; Howard et al 2011).

Finally, by offering genetic tests through the internet, genetic tests are disconnected from their usual embedding in a medical environment. The absence of medical supervision may compromise or fail to foster patient health. The fact that some DTC companies have started to integrate healthcare professionals (e.g. by asking for a prescription, or by having a consulting physician in the company) may eliminate some of the concerns that were raised with regard to the information provision and counseling, but may not dissolve the main concerns with regard to the quality and appropriateness of the test. Moreover, it is striking that most companies suggest that consumers should contact a healthcare professional for further interpretation of the test results. As this might lead to a downstream impact on the healthcare system (including the provision of other tests and interventions) based on tests that might not have been validated and that were not clinically indicated, the increasing offer to tests outside the healthcare systems challenges the organization of publically funded healthcare system.

In light of the various criticisms that were raised towards DTC genetic testing, various professional (American College of Obstetricians and Gynaecologists 2008, European Society for Human Genetics 2010, Hudson et al. 2007) and governmental organizations and advisory bodies (Gutman 2008, Federal Trade Commission 2006, Belgian Advisory Committee on Bioethics 2004, Human Genetics Commission 2003 and 2007) have issued statements and reports identifying deficiencies in the regulatory framework (Kaye 2008, European Academies Science Advisory Council) and advancing varied policy choices. We report here on two important policy discussions. Firstly, whether genetic tests should be prescription-only tests, and should be accompanied by specific legal specifications about the way genetic counseling and information is being provided. Secondly, whether and at what level genetic tests should be evaluated on their clinical utility.

A first issue of debate is focused on the way individuals can have access to genetic tests. Various EU member states (including Portugal, France and Germany) have enacted legislation that regulates the provision of genetic tests (Borry et al 2012). Without engaging here into details, these laws have emphasized the importance of the use of genetic tests in a clinical context under individualized medical supervision and after the provision of sufficient information regarding the nature, meaning and consequences of the test, as well after the consent of the person concerned. The legislation in these countries has been strongly influenced by the Additional Protocol to the Convention on Human Rights and Biomedicine 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.

A second issue of debate is focused on the regulation of genetic tests before market introduction. In the European framework, genetic tests are considered to be in vitro diagnostic medical devices and their regulation falls within the scope of the Directive 98/79 EC of the European Parliament and of the Council on in vitro diagnostic medical devices (IVD Directive). The IVD Directive, adopted in 1998, aimed to create an internal market for IVD medical devices and to ensure that such devices meet essential requirements regarding their safety and performance when placed on the market or put into service in the EU. After several years of work and two public consultations which captured the stakeholders' views regarding some of the main weaknesses of the current legal framework, the European Commission published its proposal for a Regulation, on 26 September 2012. Debates about the proposal are still going on and a vote in the European Parliament is foreseen in September 2013. The proposed IVD Regulation brings predictive genetic tests and computer algorithms within its scope and includes measures related to clinical validity such as diagnostic sensitivity, diagnostic specificity, positive and negative predictive value in its general requirements. However, the Draft Regulation stops short of requiring a pre-market assessment of companies' claims and does not require any data on clinical utility. Oversight is delegated to 'notified bodies' that conduct conformity assessments focused on the narrow issue of quality assurance. In the proposal of the European Commission, decisions on counseling and the involvement of medical professionals have been left to member states. In contrast to the proposed regulation, a country such as the Netherlands has developed legislation on population screening that aims to protect individuals against potentially harmful screenings by assessing tests before their provision to the public. Tests need a permit issued by the Dutch Minister of Welfare and Sports and those permits are provided after evaluating whether the test is scientifically sound, and in accordance with professional medical practice standards.

5.2. Participant-driven research

Recently a few 'crowdsourced' initiatives in the field of genetic research (Kaye et al 2012; Janssens et al 2012; Harris et al 2012; Prainsack 2011; Tutton and Prainsack 2011) have developed a new approach to research. This approach, which we will refer to as 'participant-centred' has been defined as 'tools, programs and projects that empower participants to engage in the research process' using interactive information technology (Kaye et al 2012). Key features of participant-centred initiatives include: a) enabling the recruitment of research participants; b) promoting interactions or communications between researchers and participants; c) providing participants with social networking possibilities; d) providing participants with certain services (e.g. return of research results); e) enabling participants to manage their preferences for personal data sharing; f) allowing participants to help drive the research agenda; and g) allowing participants to provide, and have some control over, their samples and data. Various companies (e.g. Private Access, PatientsLikeMe, Genomera, 23andme) have engaged in initiatives whereby they want to gather personal medical or health information from patients or healthy individuals and connect it to genomic information that they process. These initiatives underline how their approach facilitates participant recruitment, the information and consent process, the return of information, the recontacting of the participants and lowers the cost of doing research.

A few concerns were also raised about the development of this type of research. Firstly, the increasing provision of personal phenotypical and genotypical information from research platforms that provide the opportunity to share and compare with others, increases the already mentioned risks for privacy and confidentiality (see Section 3). Secondly, critiques were raised towards some companies that were not completely transparent towards their participants in relation to patent applications that were submitted resulting from research studies in which those participants participated (Sterckx et al 2012). Thirdly, debates revolved around the desirability of returning research results that are not validated and do not reach standards of clinical utility. This includes

concerns about the potential negative impact on individuals with regard to this type of information as well as the potential downstream impact on the healthcare system following from inappropriate retesting and additional interventions. Fourthly, critiques were also provided that studies might have been initiated without appropriate consent and approval from research ethics committees (Howard et al 2010).

5.3. Public-private partnership

Implementation of Public Health Genomics envisages various roles for commercial companies within public health services. These include involvement in public-private partnerships for data collection, storage and research and in the translation of this research into predictive and diagnostic tests for use in the clinic, direct-to-consumer or in other potential models of delivery (e.g. via pharmacists).

The need for large-scale data collection to implement Public Health Genomics has led to various public-private partnerships between governments and commercial companies, beginning with deCODE genetics in Iceland. Ethical issues include: the extent to which commercial interests rather than public interests may be driving the research agenda; privacy issues concerning sharing data with private companies, as well as its collection and storage by governments; and issues of informed consent to data-sharing, including the extent to which participants are informed of any conflicts-of-interest. For example, the establishment of large-scale public population databases that are then data-mined by commercial companies may leave participants unaware of who is doing the research and concerned about whether or not the 'researchers' are acting in their own (individual or family) interest and/or in the broader public interest.

Private investors will normally expect a return on their investment and policy-makers will need to consider whether large-scale data mining public-private partnerships are likely to deliver on their promises and whether public money is invested wisely. Concerns about the low clinical utility of genetic and genomic tests for susceptibility to common diseases should be taken into account in these decisions.

Public Health Genomics envisages that the use of personalised risk assessments within health services will transform medical practice and the relationship between patients, doctors and commercial companies. For example, following the announcement of the draft human genome in 2000, former GlaxoSmithKline Chairman Sir Richard Sykes proposed that genetic testing combined with 'pre-symptomatic' medication would lead to a transformation of medical practice and to a patient-led model for health services. This would allow patients to pay for extra medicines outside state funding, whilst keeping government-funded health services only as a basic service (Sykes, 2000). In the pharmaceutical industry's view, patient care would be improved by earlier treatment that would at the same time extend the market to those identified as predisposed to future illness (Gilham and Rowland 2001). Social scientists have described the key event in this transformation as the creation of the person 'genetically at risk', and some have expressed concern about the 'biomedicalisation' of health and illness, involving the privatization of research and a focus on surveillance and health as a moral obligation (Clarke et al 2003).

Commercial companies are enthusiastic about a new model of 'early health' involving increasing consumerism, including ordering directly over the internet bypassing medical professionals and more 'nurse-led care' (Medical Technology and Diagnostics Industry 2008). Specialist venture capital company Burrill & Company envisages;

- routine genetic screening delivered by nurse-staffed pharmaceutical outlets in supermarkets and other stores;
- widespread use of home diagnostics and remote health monitoring, with blood samples collected via smart phones and tablets;

- smart cards including electronic health records and DNA;
- consumer-driven personal health planning;
- tools to monitor medication regimens to drive compliance, and tools to measure physical activity and diet, linked to online work-outs and incentive programmes (such as paying people to lose weight);
- a shift from 'one size fits all' healthcare to personalisation, prediction, prevention/disease pre-emption and patient responsibility;
- a near-doubling of the pharmaceuticals market by 2020, including the creation of big new markets in 'wellness' and obesity, allowing healthcare companies to '*generate value*' throughout people's lives (Burrill 2008).

These changes imply a significant shift from diagnosis to prediction of disease; a reduced role for doctors and an increased role for computer algorithms and decision-support systems; and the individualisation and commercialisation of preventive health (including increased use of medication and other products such as supplements and functional foods). Relevant commercial interests include private healthcare companies, the pharmaceutical and food industries, DNA sequencing companies, and companies with an interest in cloud computing and Big Data.

In this scenario, key issues for policy makers include how to manage the relationship between public and private healthcare and how to manage, assess and regulate genetic and other information and misinformation, including the extent to which research results should lead to feedback of individual risk predictions, and the role of medical professionals. Validation of software and complex risk predictions may require access to proprietary algorithms, and regulators or technology assessors require the powers and resources to make independent assessments of companies' health claims. This issue is of relevance to the IVD Regulation currently being discussed by the European Parliament. In the case of genomics-based risk predictions of complex disease risks, clinicians cannot themselves verify the outputs of computer-based risk algorithms and may become dependent on commercial interpretations of risk and/or lack essential information about whether testing will benefit the patient, their family, or the general population.

In contrast, an alternative, more measured approach to the introduction of genetic and genomic tests, would affect much smaller numbers of people and involve the consideration of social, ethical and economic aspects within the framework of existing medical services, including, for example, existing requirements for technology assessment, fully informed consent and medical confidentiality. Commercial laboratories and commercially-marketed diagnostics kits would likely still play an important and perhaps increasing role but implementation of testing and screening services would be medically-led, with key decisions made by health service providers. This contrasts with the market-led approach of DTC genetic testing services and the mixed-economy approach of Public Health Genomics, which involves major up-front public investment in transforming public infrastructure to facilitate a commercially-driven transformation in health services.

5.4. Patenting & licensing

Patents give the patent-holder monopoly rights to commercial exploitation of an invention for 20 years or more. In theory, patents act as a reward for invention that is supposed to stimulate investment, creativity and economic growth. However, patents are often controversial as they convey monopoly rights that can be used to block competitors and restrict access to technologies. The central idea behind the knowledge-based economy is that knowledge can be patented and claimed as 'intellectual property' that is valued and traded. EC Directive 98/44/EC on the Legal Protection of Biotechnological Inventions was adopted in 1998 following a decade of controversy about the idea of 'patents on life' and led to large numbers of patent claims on human genes, leading to intense debates about impacts on access to genetic testing services.

Some companies (notably Myriad in the United States) have *genetics*-based business models that depend on maintaining a monopoly over testing for genes that they have patented. However, companies with *genomics*-based business models may be less focused on gene patents, because full genome-sequencing would require multiple licenses if each gene is patented by a different company or research institute. Both business models can involve secrecy regarding proprietary databases and the relationship between genetic variants and phenotypes. As a consequence, clinical interpretations based on publicly available information might be incomplete and insufficient and hinder clinical management (Cook et al 2012). However, the genomics business model is more reliant on open public-sector data, because much larger databases are needed. As an alternative to controlling access to data, this business model may rely on maintaining commercial confidentiality and intellectual property rights over how genomic risks are calculated using proprietary software and computer algorithms. The implementation of the new European unitary patent is an important policy development in this area, as it will influence debates about the extent to which software can be patented (Anderson, 2003).

6 Responsible Translation and Implementation

In Section 1 we have shown that there is a gap between genome research and translation in health care. The last decade of research has however brought some insights from research that are ready for implementation in health care. Translational research may imply using animal models for human disease, developing a health application till proof of principle, and regulating the product entering the market to be provided by public or private means (EWG1 Chapter 4). Some models of translation also include the development of guidelines, training, and provision of information to the public (Khoury 2007, EWG2 Chapter 4). Implementation may be defined rather similarly to translation, but we also think here about the application of useful innovations by more than a few early adopters, rather than the majority of health care workers.

In this section we will discuss how health authorities should prioritize implementation of genetic testing in health care in a responsible way, taking into account clinical utility and the needs of public, patients and physicians (EWG2 Chapter 3, EWG1 Chapter 4). Stakeholders in health care should be involved in order to develop and apply guidelines and avoid unsound applications.

Responsible translation and/or implementation (Howard 2013; Health Council of the Netherlands 2008) implies the assessment of:

(1) the scientific foundation, including the validity of the test;
(2) the significance of the health problem, relating to the number of people affected as well as the severity of the health problem;
(3) the ratio of advantages and disadvantages, including availability of interventions, clinical utility in its broadest sense;
(4) respect for autonomy, including appropriate genetic counselling and information to the public; and
(5) appropriate use of resources.

In this chapter we will come back to many of the examples mentioned in this and other EWG reports, especially to tests likely to be introduced in the near future: before conception, during pregnancy, in newborns or later in life.

6.1 Common or rare diseases

In the last decade, genome wide association (GWA) studies have provided new scientific insights, few of which are applicable in health care (EWG4 Chapter 1). Copy number variants (such as deletions or duplications) and interactions between genes or between genes and environment require further investigation. However *sequencing* the exome or genome already is already promising for introduction into health care (EWG1 Chapter 1&4, EWG4 Chapter 4). Thus we are moving away from looking for *common* variants causing *common* diseases. Instead it turns out that many common disorders in fact include subgroups that require a stratified or personalized approach (EWG1 Chapter 3). Rare diseases are increasingly seen as a public health priority. Personalized medicine promises to develop treatment for small subgroups of common disorders, such as tumour profiling followed by tailoring chemotherapy (EWG2 Chapter 4).

6.2 Interventions for high-risk genetic conditions

In the same decade, treatment opportunities for some monogenic subtypes of common complex disorders have increased. Subtypes of cancer and cardiovascular disorders that may lead to symptoms at a relatively young age and with high recurrence risks in the patient and his/her family members can increasingly be recognized. For hereditary colon cancer, apart from colonoscopy screening to detect cancer at an early stage, preventive treatment with aspirin has also turned out to

be very effective in reducing the risk of cancer development (Burn et al 2011). For several cardiogenetic conditions, implantable cardioverter-defibrillators and medication can avoid sudden death (Charron et al 2010). In EWG2 (Chapter 4.2) the use of genomics in population screening programs for these disorders is discussed; a radically new approach to prevention. It is especially for this group of conditions that the ACMG advises to always analyse the sequence of 59 genes if the whole exome or genome is sequenced, no matter what the primary clinical question was (Green 2013). Mutations in these genes can have avoidable consequences for the patient and his family members. Therefore, ACMG seems to consider that 'autonomy' should not be respected in this situation. We will come back to this below.

It may seem confusing for non-genetic experts to see papers appearing at almost the same moment that report on the one hand, that GWA studies have found many SNPs that are not significantly associated with disease risk, while on the other, more genetic counselling for the same disease is advocated (Cornel 2012). It is a major challenge to discern hype from hope (Health Council of the Netherlands 2008), and take care of implementation of tests with clinical utility while at the same time avoiding unsound applications. As discussed in EWG 2, many diagnostic tests used in medicine have a good analytic validity and clinical validity. The clinical utility of a test is defined as 'How likely the test is to significantly improve patient outcomes (www.cdc.gov) According to the Additional Protocol on Genetic testing of the Council of Europe (2008): "Clinical utility of a genetic test shall be an essential criterion for deciding to offer this test to a person or a group of persons."

6.3 Most direct-to-consumer tests offered lack clinical utility

Many of the new genetic tests aim to predict the risk of future disease. As a general promise, a better knowledge of the personal risk profile could contribute to personalized prevention. While the implementation in health care of many tests has not progressed very fast, some companies have started offering genetic tests direct-to-consumers (DTC) over the internet. The tests range from (1) single-gene tests for monogenic disorders or monogenic subsets of common disorders; (2) one or several SNPs or genetic variants found to be associated with common disorders such as diabetes; (3) genomic profiles combining gene variants or SNPs; (4) genome-wide scans for a particular range of conditions such as cancer or cardiovascular problems; and (5) tests to learn more about ancestry or traits, for example (Becker et al 2011). The majority of DTC tests on offer lack clinical utility (EWG1 Chapter 4, EWG4 Chapter 5). Thus the first criterion we mentioned above, the scientific foundation, is lacking. Furthermore, customers have to make an 'autonomous' informed choice without appropriate counselling and while truth-in-advertising may be lacking. The quality of laboratory tests may be beyond the control of the regular health care system. Building on the earlier work of the European Society of Human Genetics, the European Academies Science Advisory Council and Federation of European Academies of Medicine (EASAC/FEAM 2012), would not encourage EU citizens to use DTC genetic testing at present. They urge caution regarding DTC genetic testing in several specific respects, particiularly if individuals have symptoms or are at known increased risk, and also for prenatal screening.

6.4 How to close the gap from knowledge to implementation

The translation (or implementation) of the possibilities of 'genetics in health care' turns out to be a major challenge, not least because some 97% of genomics research funding was spent on development of knowledge to proof-of-principle (Khoury et al 2007). A comprehensive research agenda is needed to move human genome discoveries into health practice in a way that maximizes health benefits and minimizes harm to individuals and populations. For genetics to become further integrated into regular health care, many elements in a chain are needed, including health technology assessment, development of professional guidelines, teaching medical professionals and public awareness (Cornel 2012). If a new test has a high predictive value and interventions are

available to reduce the risk, evidence based guidelines need to be developed (phase 2 in Khoury's model of phases of translation), dissemination and diffusion of the guidelines are needed (phase 3) so that in the end (in phase 4) the 'real world' health outcomes of a genomic application in practice can be evaluated (Khoury 2007).

6.5 Genetic testing and reproductive options

So far we have discussed testing in the interest of the individual. In ethical terms this is a straightforward situation, where balancing the pros and cons will focus on the interest of this individual (beneficence, non-maleficence, privacy).

If parents (to be) consider a genetic test, they may look for information on the risk that their (future) child will have a serious genetic disorder. They may use genetic testing to decide between reproductive options, such as (not) getting pregnant, using prenatal diagnosis and termination of pregnancy in case of serious fetal disorders, using donor gametes, accepting the risk, etc. In these decisions the ethical framework of the clinical geneticist has always put individual autonomy at the centre. Helping couples to make their own informed choice is a very important ethical principle in genetic counseling, as can be recognized in the fourth element of the definition of genetic counseling of the American Society of Human Genetics (1975):

> "Genetic counseling is a communication process which deals with the human problems associated with the occurrence or risk of occurrence of a genetic disorder in a family. This process involves an attempt by one or more appropriately trained persons to help the individual or family to: (1) comprehend the medical facts including the diagnosis, probable course of the disorder, and the available management, (2) appreciate the way heredity contributes to the disorder and the risk of recurrence in specified relatives, (3) understand the alternatives for dealing with the risk of recurrence, (4) choose a course of action which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards and act in accordance with that decision, and (5) to make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence of that disorder."

Obviously the reproductive options have to be considered within the possibilities of laws and professional guidelines in their country.

'Responsible translation/implementation' will, in the context of reproduction, imply that information is available for couples and that health care workers can explain options and help them to make their own decisions without coercion (4^{th} criterion above). The scientific validity and severity of the health problem clearly need to be taken into account (1^{st} and 2^{nd} criterion). The balancing of pros and cons is even more dependent on personal and societal values (3^{rd} criterion). The appropriate use of resources (5^{th} criterion) may be difficult to take into account here, because a free and informed decision is the primary goal in reproductive applications of genetic testing. On the other hand, if choices between different techniques for prenatal diagnosis, pre-implantation diagnosis etc, have to be made, resources will play a role.

6.6 Whole genome sequencing

At present, many clinical genetic centres in the EU can perform whole genome (exome) sequencing for patients that have a severe medical problem with unresolved but likely genetic etiology. The number of cases for whom WGS can be offered is still limited. Discussions on the use of WGS include questions of what to analyse and what to report. Apart from an answer to the initial clinical question, unsolicited findings of clinical relevance may be encountered (such as a high risk of cancer when

looking for the cause of mental retardation). Should bioinformaticians in the laboratory be allowed to analyse parts of the genome if this is not needed for the initial clinical question? Should laboratories report only results of proven clinical utility or anything they find of potential clinical relevance? Should clients be allowed to consent on what (or what not) to report back? Can parents decide for their child what should (or should not) be reported?

Some advocate that if the entire genome is sequenced, the analysis should by default include more than the initial question, thus also using the technology as an instrument for 'opportunistic screening'. Others expect that newborn screening will be used as the appropriate moment to start interpreting the genome. As many health care workers today still lack genetic knowledge for every day practice, communication and coordination between laboratory (bioinformaticians), physicians and the public is urgently needed. A tsunami of results implies the risk of information overload and missing the most relevant opportunities.

The European Society of Human Genetics recently recommended to target as much as possible. The analysis of genomic data should first of all be led by the initial clinical enquiry. Furthermore, informed consent should be sought for the reporting of unsolicited findings. This stance is clearly different from the American College of Medical Genetics, which recommends investigating 59 genes in which mutations can lead to serious and avoidable health consequences in all cases where whole exome or genome sequencing is performed. The EWG4 supports the ESGH view that 'nothing about us' should be done 'without us', or in other words, that informed consent should be sought where possible (See also Chapter 4). We recognize that some unsolicited findings may require return of results to individuals undergoing WGS because of consequences for the individual screened and/or his or her relatives, but consider it premature in 2013 to start looking for mutations beyond the initial clinical problem. Informed consent procedures must be developed for WGS in the clinic (Rigter *et al.* 2013).

After these rather general aspects, we will now discuss several specific fields of testing in public health genomics.

6.7 Newborn screening

Newborn screening (NBS) programmes in the EU nowadays aim to identify one to 30 treatable conditions (Loeber et al 2012). Depending on health care structure, available funds, local politics, input from professional groups, parent groups, and the general public, this introduction has led to different approaches in the way the screening programmes have been set up, financed and governed. The diversity is large. Confirmatory diagnostics and follow-up show large discrepancies. DNA testing is integrated as a final step in some programmes for cystic fibrosis screening, but cheaper tests (esp. tandem mass spectrometry) are often used. Many have suggested integrating whole genome sequencing in NBS (EWG1 Chapter 2; EWG2 Chapter 2.3), or even replacing it.

In a recent expert opinion document, the first condition advised to start a newborn screening program for is congenital hypothyroidism (Cornel et al 2013). This is usually not a genetic condition, and cannot be diagnosed by whole genome sequencing. Therefore NBS cannot be replaced by WGS.

Furthermore, the reported cost of the newborn screening procedure in 2011 in the EU ranged from €0.46 per newborn (Serbia; screening for 2 conditions) to € 43.24 (the Netherlands; screening for 17 conditions) (Burgard et al 2012:27), while sequencing and analyzing the data is much more expensive. Therefore, criterion 5 is currently not fulfilled.

Furthermore, the interpretation of DNA data in a population of healthy newborns is a challenge. The genotype-phenotype relationship in metabolic conditions is not straightforward. In the case of Pompe's disease for instance, there is a large clinical diversity in patients with functionally the same

genotype (Kroos et al 2012). An agenda for the responsible translation of WGS in NBS would include determining the prognostic value of mutations identified. NBS for neonatal intensive care units could be a first step to integrate WGS in health care (Saunders 2012).

6.8 Big data and newborn screening

A separate issue is the storage of the sequence. One could argue that the genome of a newborn could be sequenced once, and analysis later in life could focus on disorders relevant at that age. Storage of genetic information raises questions of governance and privacy protection (EWG4 Chapter 4). Furthermore, if the price of genome information is decreasing fast, it could be considered to sequence again when relevant, instead of storing. In the view of this working group, storing the whole genome sequence information of newborns is premature today. Their rights to privacy and to consent for themselves once they are adult have to be respected. Policy makers need to consider not only the information content of the genome but also its role as a biometric which can be used to identify and track individuals and their relatives. Storage will also be expensive.

6.9 Non invasive prenatal testing (NIPT)

For some genetic tests in the prenatal setting, free fetal DNA from maternal blood can be analysed. This is a relatively new development that is currently used for the detection of rhesus positive foetuses in rhesus negative mothers and in prenatal diagnosis in high risk pregnancies. Also screening for Down syndrome and other fetal chromosome anomalies is developing in a non-invasive manner (EWG2 Chapter 2). The test validity of NIPT is much better than the usual first trimester combination testing (sensitivity and specificity in NIPT both >99%), which implies that fewer amniocenteses would be needed and more accurate results would be provided. Currently, commercial companies offer NIPT for Down syndrome in some European countries, but integration in existing national health system/ public health programmes is conceivable. There is an urgent need for quality assessment (EWG2 Table 2.1). Non invasive prenatal testing may be used for an increasing number of health problems, both for health promotion (as in rhesus screening) and to offer reproductive choice (as in testing for serious chromosome anomalies). Which conditions should be included, where to draw the line?

A second issue is that prenatal screening programmes for chromosome anomalies followed several steps, which took days or weeks, thus making the 'informed decision making' a process. Some argue that NIPT would make a one-step-screening possible, which might lower the threshold for uptake. Thus couples might accept a test without considering what the consequences might be (such as having to choose whether or not to terminate a pregnancy if a serious chromosomal anomaly would be detected). The 4th criterion above requires that couples should not simply accept the test-offer because it is cheap, fast and easy.

Responsible use of NIPT requires a step-by-step increase of populations to which the tests are offered, including quality assessment and evaluating client experiences as well as preferences for further development. Also the disorders included need a step-by-step approach to enable learning from earlier experiences. The five criteria must be taken into account when considering using the technology for other disorders.

6.10 Adult carrier testing

As discussed in EWG2 (Chapter 2), recessive mutations can be identified in future parents thus allowing them to make informed reproductive choices, some of which will prevent the birth of an affected child. Public health programmes exist in several populations targeting one disease (Thalassemia in Cyprus, Tay Sachs in Ashkenazi Jews), but it can be envisaged that WGS technology

will make testing for many other disorders possible. Who will decide on the selection of diseases that the test can offer, will public health authorities take responsibility for these programs or will commercial operators (such as www.counsyl.com) dominate the field? Integration of the five criteria mentioned at the start of this section can only be expected if public health leadership takes responsibility for the implementation of scientifically sound testing for serious conditions, allowing future parents to make their own informed choice whether or not to participate in the screening.

7 Conclusions - Ethical, legal and social aspects of Public Health Genomics

7.1 Concept of Public Health Genomics

The definition of public health genomics (PHG) that was used in this report is: "The responsible and effective translation of genome-based knowledge and technologies into public policy and health services for the benefit of population health" (Lal et al 2011). Its proper form and content are still under construction. New technical and scientific developments have created new potential applications of genomic technologies for the health care sector, both for individual care and public health. Some original promises of the field of PHG have not been substantiated while other potential applications are developing fast. Thus there is a need to discern between hope and hype. Testing c*ommon* genetic variants for *common* disorders has not turned out to have clinical utility so far. However, in 5-10% of common disorders, high-risk genetic variants are implicated. For some of them interventions are available, so testing for these rare variants needs (further) implementation. For rare genetic disorders which affect all in all up to 5-8 % of the population, screening programs and individual whole genome sequencing hold clear promises, while an unspecific population-wide genetic screening cannot be substantiated on the basis of current knowledge.

7.2 Legal and ethical aspects

PHG includes research, policy and health services, each of which has its own ethical, legal and societal aspects. The approach of PHG requires a delicate balancing of public interests (collectivism) and interests of the individuals (individualism). Responsible implementation implies the assessment of scientific foundation, including the validity of the test, the significance of the health problem, relating to the number of people affected as well as the severity of the health problem, the ratio of advantages and disadvantages, including availability of interventions, clinical utility in its broadest sense, respect for autonomy, including appropriate genetic counselling and information to the public, and appropriate use of resources.

Scientific developments in the field of public health genomics demand large biobanks and databases to better understand the role of the genome in disease etiology. For instance, the UK plans to sequence the genome of 100,000 individuals for research purposes using data and infrastructure of the national health service, combined with clinical applications in some circumstances. Storage of, access to and protection of data, informed consent and the question of what to feed back to participants needs policy development.

Highly predictive genetic variants may be encountered as unanticipated findings in research and in whole genome sequencing for other clinical indications, thus raising questions about boundaries between research, diagnostics and screening. Furthermore, the balance between the 'right not to know' and the 'duty to inform' needs policy development.

7.3 Assessment of quality of genetic tests

In vitro diagnostic laboratory test *products* are currently regulated under the IVD Directive, and a proposal for a new IVD Regulation is on the EU Parliament's agenda. The Draft Regulation stops short of requiring a pre-market assessment of companies' claims and does not require any data on clinical utility. Oversight is delegated to 'notified bodies' which focus on the narrow issue of quality assurance. *Clinical utility* should be central in decisions on the implementation of genetic testing possibilities. Testing for *rare* disorders occurs in accredited genetic laboratories, where laboratory developed tests can be used (without conformity assessment) and the quality is guaranteed by the complete quality system, including training of personnel and integration in the health care service.

Whole genome sequencing for clinical purposes is developed both in public and commercial laboratories.

Current direct to consumer offers (DTC) of predictive genetic testing for common diseases generally lack clinical utility. Therefore EU citizens should not be encouraged to use DTC for this purpose. Special caution is needed regarding DTC genetic testing if individuals have symptoms or are at known increased risk; as well as for prenatal screening and preconception carrier screening, since genetic counselling may not be available.

7.4 Quality of genetic services

If PHG is to be implemented in a responsible way, health care *services* must be developed further to contribute to public awareness, training of non-genetic health care workers, provision of genetic information and counseling.

A comprehensive agenda for translation of genomics knowledge in health care is needed, including the development of guidelines, training health care professionals and evaluating outcomes in real life. While health care is the responsibility of EU member states, support at EU level could provide an added value, since challenges are similar throughout Europe.

Genetic testing for monogenic subtypes of common disorders that lead to a high risk at a young age, and where interventions are available to reduce the risk should be prioritized for implementation in health care. Rare treatable conditions can be identified in newborn screening. Current prenatal screening programs can be improved using non-invasive prenatal screening, with high sensitivity and specificity, and less invasive procedures. On the other hand this would most likely also accelerate the ethical problems already connected to prenatal diagnosis and screening and the choices that have to be made in this context.

7.5 Access to GT services (equity)

'Responsible' implementation of PHG implies that the benefits should be accessible to all on the basis of their vulnerabilities and needs. Fast developing fields such as genomics may profit from public-private partnerships and involvement of commercial companies. However, health service providers and policy makers should prioritize resources with regard to the clinical utility of the offered services rather than following the market-led approach of direct-to-consumer genetic testing so far.

7.6 Whole genome sequencing as screening (for healthy individuals & in diagnosis)

EWG4 supports the option to use whole genome analysis only for specific purposes (not routine screening): the aim should be to restrict the amount of generated data, avoid unsolicited findings, limit privacy problems and ease the burden of information. An agenda is needed for the responsible implementation of whole genome sequencing in those subpopulations (mentioned in 7.1) where benefits are most likely to be delivered. The predictive value of mutations must be assessed. Economic aspects must be evaluated. Newborn screening by whole genome sequencing is not recommended.

7.7 Whole genome sequencing and research

Storing the whole genome sequence information as a standard means of health care is premature today and not recommended. A new genetic test can be performed when there is a new reason for further testing.

Especially for minors, the rights to privacy and to be able to consent for themselves once they have reached adulthood, have to be respected.

Not only the information content of the genome but also its role as a biometric source which can be used to identify and track individuals and their relatives, has to be considered. This raises specific ethical and social issues which need to be solved prior to the introduction of a measure such as WGS.

Furthermore, data storage will be expensive and difficult to organize with a need to guarantee data protection standards for long periods of time.

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Biographies

Expert Working Group 1

Prof. Johan T. den Dunnen (Leiden University Medical Center, The Netherlands)

Johan T. den Dunnen (PhD) is professor of Medical Genomics, working in the departments of Human and Clinical Genetics at the Leiden University Medical Center (Leiden, The Netherlands). He is a trained biologist, specialising in molecular biology/molecular genetics. As head of the Leiden Genome Technology Center (LGTC), LUMC's genomics and transcriptomics facility, he focuses on the development and application of high-throughput genome technology in research and diagnosis of genetic disease. His current focus is on next generation sequencing and data analysis pipelines, especially exome/genome sequencing and RNA-expression profiling, gene variant databases (the LOVD platform) and biosemantics.

Dr. Xavier Estivill (Centre Genomic Regulation/ Pompeu Fabra University, Barcelona)

Xavier Estivill graduated in Medicine in 1979, specialising in Haematology, and has a doctorate in Medicine (MD) from the Universitat Autònoma de Barcelona (1987) and in Philosophy (PhD) from the University of London (1995) for studies on the genetics of cystic fibrosis. He is Senior Group Leader at the Centre Genomic Regulation (CRG), and Associate Professor of the Pompeu Fabra University (UPF) in Barcelona. He directed the Genes and Disease Program between 2002 and 2012, the Genetics Service of the Clinic Hospital (1991-1997) and the Cancer Genetics Institute (1991-2001) in Barcelona, and was Visiting Scientist at the Hospital for Sick Children in Toronto (2001-2002). He has been board member of the European Society of Human Genetics, sits on the board of several human genetics journals, and is member of several scientific advisory boards of several international institutes and funding agencies.

His group has contributed to the understanding of many human genetic disorders. The current work of his group is focused on the analysis of human genetic diseases, with a special interest in the role of structural variants, epigenetic changes and non-coding RNAs. His group is applying next generation sequencing technologies to reveal the genetic basis of complex and rare diseases. He coordinates the European action to analyse the genetic variability of disease in Europe (GEUVADIS). Recent achievements of his group include the identification of genetic variants associated with psoriasis and several psychiatric diseases, and the description of toxicity of small RNAs in Huntington's disease.

Prof. Milan Macek Jr. (Charles University, Czech Republic)

Professor Milan Macek Jr. is the chairman of the largest academic medical/molecular genetics institution in the Czech Republic, which also comprises a research / diagnostics reproductive genetics centre /ublg.lf2.cuni.cz/. He is also the past President of the European Society of Human Genetics (www.eshg,org), board member of the European Society for Human Reproduction and Embryology (ESHRE.com) and of the European Cystic Fibrosis Society (ECFS.eu). His institute is a "clearing centre" for dissemination of knowledge in genetics gthered within various international European projects, such as CF Thematic Network, EuroGentest, EuroCareCF, Techgene or RD-Connect to Central and Eastern Europe. Prof. Macek did his first postdoc at the Institut of Human Genetics in Berlin, continued as a postdoctoral fellow at the McKusick-Nathans Centre for Genetic Medicine, Johns Hopkins University in Baltimore and during that time he was also a fellow at Harvard School of Medicine in Boston. He was the local host of the 1995 HUGO Mutation Detection Course in Brno, the 2005 European Society of Human Genetics conference and of the 2008 European Cystic Fibrosis Conference, both held in Prague. Prof. Macek is national coordinator of Orphanet (www.orpha.net),

an active member of Eurogentest (www.eurogentest.org), has been the chief advisor of the Czech EU Council Presidency under which the "EU Council recommendation on an action in the field of rare diseases" was adopted in June 2009. He also serves at the EUCERD.eu committee on rare diseases.

Prof. Irmgard Nippert (Westfaelische Wilhelms-Universitaet, Muenster, Germany)

Professor Irmgard Nippert is a medical sociologist by training. She has been conducting national and international research projects for more than three decades, evaluating the translation and application of medical knowledge in transition from research into medical practice – with an emphasis on genetics. She has been awarded numerous international and national funding by peer reviewed funding institutions such as the European Commission (EC), the German Research Foundation and the German Ministry of Education and Research. She is currently coordinating the global "Genetic Testing in Emerging Economies" (GenTEE) study in collaboration with the EC's Joint Research Centre Institute for Health and Consumer Protection. She has been work package leader in the EuroGentest Network of Excellence (2005-2010) and is an adjoined member of EuroGentest2 (2010-2013). She is a university professor at the Women's Health Research Unit, affiliated with the Department of Human Genetics, Medical School, Westfaelische Wilhelms-Universitaet Muenster in Germany.

Expert Working Group 2

Prof. A. Cecile J.W. Janssens (Emory University, Atlanta, USA)

Cecile Janssens is professor of translational epidemiology at Emory University, Atlanta, USA. Her research concerns the translation of genomics research to applications in clinical and public health practice, with a focus on the predictive ability and utility of genetic testing for common diseases. Cecile Janssens has published over 150 papers in international scientific journals and received three prestigious personal grants, most recently the ERC Starting grant. Before moving to the USA, she was chair of the Dutch Association of Community Genetics and Public Health Genomics and board member of the Netherlands Association for Human Genetics. She still is an active member of the Health Council of the Netherlands.

Prof.em. Inge Liebaers (Belgium)

Inge Liebaers is an MD, PhD, pediatrician and clinical geneticist. She was the Director of the Center for Medical Genetics at the Vrije Universiteit Brussels (VUB), Professor of Medical Genetics and now Emeritus . She was the President of the National Council for Anthropogenetics. She is a member of the Belgian Advisory Committee on Bioethics and of a subcommission on Public Health Genomics of the National Health Council. She was the president of an expert group of the Council of Europe which led to Rec (2010)11 of the Committee of Ministers to member states: 'The impact of genetics on the organisation of health care services and training of health professionals'. Together with the Center of Reproductive Medicine of the VUB, she developed one of the largest Preimplantation Genetic diagnosis (PGD) clinics in Europe.

Prof. Borut Peterlin (University Medical Center Ljubljana, Slovenia)

Borut Peterlin is head of the Clinical Institute of Medical Genetics, University Medical Center Ljubljana and professor of Human Genetics at the Medical faculty Ljubljana, Slovenia. He is a board member of European Society of Human Genetics and member of it's two committees: the Public and Professional Policy Committee and the Genetics Services Quality Committee. He was a member of SCHER (Scientific Committee on Health and Environmental Risks) and EUCERD (European Union

Committee of Experts on Rare diseases) European Comission, as well as member of Committee of experts on the impact of genetics on the organization of health care services and training of heath professionals, Council of Europe. He coordinated and participated to several FP and national research projects in the field of human genetics and omic technologies and published over 140 papers in international scientific and professional journals.

Dr. Iñaki Gutiérrez-Ibarluzea (Basque Office for HTA)

Iñaki Gutiérrez-Ibarluzea BSc, MSc, PhD is the Knowledge Manager and Coordinator of the early awareness and alert system of Osteba, the Basque Office for HTA. He is member of the HTAi ISG on information resources, the HTAi ISG group on Membership and dissemination and chairs the HTAi-ISG on disinvestment of technologies of low-added value. He has collaborated in several European Union funded projects including: InnoHTA, EunetHTA, PHGEN I and II and Health ClusterNet in a number of different roles. He also coordinates a variety of projects at the Spanish level such as: GENTecS or Information resources group. He is currently the chairman of EuroScan, the International Network for the identification and assessment of new and emerging health technologies. He is also professor at the Nursing School of the Basque Health Service Osakidetza and collaborates with the University of the Basque Country and the University Oberta of Catalonia in different academic activities. He was actively involved in the e-text on HTA promoted by the ISG on information resources and in the development of the HTAi vortal on information resources. At the Spanish level he coordinates the Spanish Group of Agencies for the Identification and assessment of new and emerging technologies and is member of the groups for the assessment of obsolete technologies and the development of post-introduction systems for the assessment of health technologies leaded by the Galician Agency (Avalia-T).

Expert Working Group 3

Dr. Catherine Bourgain (INSERM, France)

Catherine Bourgain is a researcher in genetic epidemiology at INSERM (French national institute for health and medical research) and president of the Fondation Sciences Citoyennes, a civil society organization campaigning for participatory research and democracy in science.

Dr. Eugenijus Gefenas (Vilnius University)

Eugenijus Gefenas is an associate professor and director of the Department of Medical History and Ethics at the Medical Faculty of Vilnius University. He is also a director of the Lithuanian Bioethics Committee.

Alastair Kent, OBE (Genetic Alliance UK)

Alastair Kent is the director of Genetic Alliance UK. This is an alliance of over 160 patient organizations which seeks to promote public understanding of the needs of patients with all forms of genetic disorders, ranging from extremely rare conditions arising from a mutation in a single gene to common complex disorders where genetic, environmental, lifestyle factors combine with other factors to contribute to the development of the condition. The Alliance advocates for sustainable high quality biomedical research that will translate into products, services and support for all who need to benefit from greater genetic and genomic insights.

Prof. Fred Paccaud (University of Lausanne)

Fred Paccaud is professor of Epidemiology and Public Health, University of Lausanne, Director of the Institute of Social and Preventive Medicine, Lausanne, Director of the Swiss School of Public Health, Zürich.

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