

# The 'thousand-dollar genome': an ethical exploration

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**Monitoring Report Ethics and Health 2010**

**CENTRE FOR ETHICS AND HEALTH**

*The 'thousand-dollar genome': an ethical exploration*  
Edition of the Centre for Ethics and Health  
ISBN 978-90-78823-16-2

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Preferred citation:  
Health Council of the Netherlands. *The 'thousand-dollar genome': an ethical exploration*  
Monitoring Report Ethics and Health, 2010/2. The Hague: Centre for Ethics and Health, 2010

Publicatienummer Health Council of the Netherlands: 2010/15E.

This publication can be downloaded from [www.ceg.nl](http://www.ceg.nl) / [www.healthcouncil.nl](http://www.healthcouncil.nl) / [www.rvz.net](http://www.rvz.net)

To the Minister of  
Health, Welfare and Sport

Dear Minister,

Sequencing an individual's complete genome is expected to be possible for a relatively low sum within a few years. This creates new opportunities for medical research. Improved understanding of the function of specific fragments of the genome, greater knowledge about the meaning of genetic variation, and greater insights into the interaction between genes and environmental factors will contribute to improvements in preventive and curative care. However, diagnostic testing and screening based on whole genome sequencing will also give the so-called 'thousand-dollar genome' a place within healthcare.

This monitoring report describes a number of potential applications, some closer by and potentially more realistic than others. One application that may be expected in the short term is genome-wide diagnostic testing for poorly understood diseases. Searching the entire genome for a genetic cause will often allow a diagnosis to be made. This is already being done using techniques that look less deeply into the genome. An application that is currently less useful is actively analysing an individual's 'personal genome' without medical indication. The advantages some expect from this depend on the realisation of the ideal of personalised forms of prevention and treatment (personalised medicine). This remains largely in the future.

This monitoring report is an ethical exploration. It lists the potential advantages implementation of the thousand-dollar genome may bring to healthcare, but also points out the possible disadvantages. After all, genome-wide tests can also deliver information that is a burden or harmful for individuals involved. Difficult ethical (and legal) questions are raised regarding, among other things, informed consent, the right to not know, genetic testing in children and protection of privacy. In essence, these themes and questions are not new; their scale in this context, however, is.

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Date  
December 21, 2010  
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Subject  
Presentation Horizon  
scanning report

The report emphasises that the debate on the responsible implementation of genome-wide diagnostic testing and screening is urgent and requires broad discussion. Developments are quick and there are all manner of factors affecting the rate of progress. These include commercial interests of companies already active in the direct to consumer test market, those of medical research, the widely held belief that timely information about potential health risks is always useful, and the idea that being able to obtain such information is something that people should decide on for themselves.

An important message is also that the normative frameworks we traditionally use to view developments in the field of predictive medical testing do not appear to be suited for the developments outlined in this publication. Familiar distinctions, such as those between diagnostic testing and screening are becoming increasingly blurred and are therefore losing their capacity for guidance. This makes the necessary debate even more complex: it will also need to address the question of whether at least some normative principles need reviewing.

The conclusion is that we are at the threshold of a development that is in many ways uncertain, but that has potentially major consequences for healthcare as well as society as a whole. It will be up to the government to find the right balance between protecting citizens from dangerous applications and promoting useful new forms of diagnostic testing and screening.

Sincerely,  
(signed)  
Professor L.J. Gunning-Schepers

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# Summary

Sequencing an individual's complete genome is expected to be possible for a relatively low sum ('one thousand dollars') within a few years. Sequencing is determining the order of base pairs that make up the genome. The result is a library of three billion letter combinations. Cheap whole genome sequencing is of greatest importance to medical scientific research. Comparing individual complete genomes will lead to a better understanding of the contribution genetic variation makes to health and disease. As knowledge increases, the 'thousand-dollar genome' will also become increasingly important to healthcare. The applications that come within reach raise a number of ethical questions. This monitoring report addresses the issue.

## Analysing the entire human genome

Whole genome sequencing (WGS) can lead to whole genome analysis (WGA), in which the meaning of the raw data obtained during sequencing is fleshed out. This is done using software integrating the latest scientific insights into the relationship between genes and health. Filters may be used to selectively examine certain parts of the genome (*targeted analysis*), for example when diagnosing diseases with a known genetic substrate. Use of filters helps limit the amount of non-relevant information. Using this approach, WGS-based diagnostic testing yields results that are not different from diagnostic testing with existing methods, such as DNA chips. If WGS becomes cheap enough in future, it will likely become the standard approach.

## Genome-wide diagnostic testing

WGA (complete sequence analysis) is also expected to play a role in healthcare, specifically the diagnosis of diseases for which the genetic background is not yet (or insufficiently) clear. Searching the entire genome will often allow a diagnosis to be made. This approach was recently already implemented, but using less powerful techniques. Genome-wide diagnostic testing inevitably means that far more genetic information about the patient is revealed than is necessary for answering the help demand. Among other things, this raises questions about the feasibility of informed consent, the possibility to shape the 'right not to know' and the limits to the requirement to inform patients. What should happen with the (raw) sequencing data afterwards? Should it be stored? Is it allowed to be destroyed? What about the analysis findings (genetic information): should all unsought for findings also be saved? What about

genetic information not desired by the patient, and therefore not supplied to him or her? Finally: can a doctor be expected to actively inform the patient if new scientific knowledge means past that data obtained from past whole genome analysis may be viewed in a new light?

## **Genome-wide screening**

Some commentators expect full genome sequencing and analysis for every individual will be worthwhile in a few years. This would be performed without a concrete medical indication, meaning it is screening rather than diagnostic testing. Whole genome screening creates a personal genomic database ('personal genome') that can subsequently be used to deliver 'personalised medicine' to individual patients. While the first steps in this direction have already been taken (particularly in the field of pharmacogenetics: 'personalised medication'), this largely remains something for the future. According to some, analysing the personal genome would ideally be done when people reach legal age. The individual can then decide for himself whether or not to take part in this form of screening, and it is still early enough in life to benefit sufficiently. The usefulness may consist of lifestyle advice, treatment and prevention tailored to the personal health profile, but also of risk information that could affect reproductive decisions. In addition to the (currently largely hypothetical) advantages of analysing the personal genome, there are also all too real disadvantages to obtaining information that could be a burden or even harmful. Disadvantages include worry caused by (still) unclear findings and the resulting – often unnecessary – contacts with healthcare. 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. However, as soon as WGS/WGA becomes cheap enough, commercial parties will likely see a market. Whole genome tests are already commercially available, albeit currently only implementing methods that only examine small, common variations in the genome. The existing commercial availability of preconception testing for recessive genetic conditions to individuals and couples who wish to have children is also a potential area for expansion. Application of WGS in this context can easily lead to the question of why analysis should be limited to finding out about carrier risk status. If removing filters is enough to obtain a whole genome analysis, the question is not longer what we do, but what we do not want to know about ourselves.

## **Genome-wide screening of newborns**

Some advocates of the concept of tailor-made medicine suggest that analysing personal genomes is best done as early as possible in life, namely at birth. Practically, this would entail expanding the current neonatal heel prick screening based on WGS/WGA. Questions other than those already listed regarding the balance between advantages and disadvantages arise. The question is also whether analysing the complete genome of a child without a medical indication is acceptable, given all kinds of information about genetic characteristics will become known that is only important far later in life. Don't children have the right to decide



whether or not they wish to know about the strengths and weaknesses in their own genome later in life? Current heel prick screening does not face this problem; it focuses solely on conditions where timely treatment or prevention (often a diet) can prevent significant health harm to the child. However, there is already a trend towards expanding neonatal screening. According to the American *President's Council on Bioethics*, the underlying interests – particularly those of scientific research – are so great that the scenario of genome-wide screening of newborns will be difficult to prevent.

## **Genome-wide prenatal diagnostic testing and screening**

It is now no longer a fantasy that the full genome could be sequenced even earlier in life, namely during pregnancy. This would not be done in the interests of personalised medicine, but within the context of prenatal testing focused on allowing informed decisions about whether or not to carry the pregnancy to term. If this is done based on a possible health problem in the foetus, it is referred to as prenatal diagnostic testing; a routine offering is referred to as prenatal screening. Genome-wide diagnostic testing is already being used (using current techniques) to help clarify unexplained ultrasound findings. However, the scope of prenatal screening is also expected to be broadened. Eventually, those who want as much information as possible about the foetus will no longer be happy with anything less than the complete genome. The question arises of whether the primary goal of prenatal screening will not be threatened. The broader the test, the more diverse the potential outcomes, the more difficult it will be to enable the pregnant woman (and her partner) to provide true informed consent. Will this not lead to almost every pregnancy delivering a finding that forces the pregnant woman to decide on whether or not to abort, even if only because of a finding whose meaning is not yet clear? Finally, this scenario creates a new and currently unaddressed problem: children born after whole genome diagnostic testing or screening already have a fully analysed genome. The question remains whether or not this harms the right of the future child to decide for him or herself.

## **Genome-wide screening of embryos**

The introduction of increasingly broad testing also applies to the screening of embryos created for an IVF treatment (pre-implantation genetic screening, PGS). This involves the selection of embryos that qualify for implantation into the uterus. Currently, this is conducted largely based on morphological characteristics that appear to be important for a chance at a successful implantation and pregnancy. More informative tests that look at chromosomal abnormalities are currently being developed. Certain experts believe that it will eventually be possible to conduct genome-wide analysis on IVF embryos. This seems to shift the goal of screening from selecting the embryo which has the best chance of growing into a child, to selecting an embryo that will grow into a child that is as good, or at least as healthy as possible. If a choice must be made, is it not the responsibility of doctors (and future parents) to choose the embryo with the best health prospects? However, it would also mean that the

entire genome of an embryo that will potentially grow into a child has already been charted. The question is whether this is acceptable.

### **Existing review frameworks under pressure**

The questions raised by the potential implementation of the thousand-dollar genome are not all new. The scale of the challenges is, however. More important is what is happening with the normative frameworks normally used to thematise and answer such questions. They are under pressure, starting to overlap or run into each other. This applies primarily to the difference between diagnostic testing and screening. If whole genome sequence analysis is used to determine the genetic background of a poorly understood health problem in an individual patient, the motive remains diagnostic testing. However, given the fact that at most a tiny amount of all health information this delivers will have anything to do with the specific problem being investigated, the procedure also closely resembles a form of (undirected) screening. If this is the case, should such research not be reviewed using the normative framework developed for screening?

A second issue is how analysing personal genomes without a medical indication relates to the normative framework developed for screening. Because it is impossible to grasp what predictive information genome-wide, undirected screening may yield, it is impossible to determine what the balance of advantages and disadvantages for the individuals to be tested will be. In the context of the normative framework, it would appear not to be a good idea. But does that framework provide the correct perspective for reviewing the analysis of a personal genome? Reasoning from the ideal of personalised medicine, everyone is a patient from cradle to grave. The distinction between screening and patient care then loses all meaning. Or maybe analysing the personal genome is an issue of the right of individuals to obtain genetic information relating to themselves? The discussion on this subject will inevitably receive a fresh impulse if a market for sequencing and analysing personal genomes develops.

The distinction between reproductive and non-reproductive screening is also becoming blurred. Until now, these were separate worlds with their own normative frameworks and principles. For non-reproductive screening, the emphasis is on health gains and a certain amount of directiveness is not seen as problematic: it is fine to draw people's attention to their responsibility for their own health. Reproductive screening, on the other hand, traditionally has a strong focus on the highly personal character of reproductive decisions with an ideal of professional non-directiveness. The application of genome-wide tests would lead to a blurring of the borders between these two worlds, leading to difficulties determining which normative principles should guide decision-making.

In conclusion, familiar normative frameworks appear to lose at least part of their organising capacity and guiding character. Although some of the developments discussed are problematic when viewed from within these frameworks, there is also room to ask whether

review or recalibration of these frameworks is necessary, should we wish to continue providing guidance for the application of scientific knowledge in healthcare.

### **Debate and new guidelines required**

Further reflection on the developments outlined above and the normative implications thereof for all parties involved, including clinicians, scientists, jurists, ethicists, patient organisations and policy makers is of great importance. To begin with, there is a need for guideline development by the professions involved in the application of genome-wide diagnostic testing in adults, children and foetuses. The most current question is how to responsibly deal with unsought for findings of such diagnostic testing. Given the complexity of the matter, in both normative and scientific terms, there is also a need for more comprehensive reflection and debate.



# 1 Introduction

In 2003, the first practically complete inventory was taken of the building blocks of the human genome. Since then, scientists have worked to develop a cheap method to quickly and reliably sequence an individual's entire genome. This has been called the 'thousand-dollar genome'.<sup>1,2</sup> Following global efforts, success appears to be in sight. This opens doors to a wealth of knowledge that will provide a major impulse to scientific research into the meaning of the human genome. This is also an important development for the healthcare field: if it becomes possible to quickly and cheaply sequence and analyse everyone's 'personal genome', it clears a path towards personalised medicine.

At the same time, it raises ethical, legal and social questions. Is analysing an individual's entire genome allowable? Under what circumstances and in what way? This monitoring report addresses the issue. The goal is to outline the normative dimensions relating to the thousand-dollar genome in broad strokes, thereby providing the building blocks for the necessary debate on the acceptable and careful implementation thereof.

## 1.1 Futures

The first goal of the 'thousand-dollar genome' is to obtain new knowledge. Currently, knowledge about the functions of specific fragments of the human genome and the meaning of variations therein is still limited. However, if the complete genome becomes available for a large number of individuals, comparisons can become a powerful tool to gain better insights. As knowledge increases, the 'thousand-dollar genome' will become increasingly important to healthcare. That is the secondary goal, which can for now only be realised in part due to the still rudimentary knowledge.<sup>3,4</sup> Once an individual's complete genome has been sequenced – meaning the order of the chemical building block (base pairs) of the genome has been determined – it can be fully or partially analysed. In this analysis, the genomic variation found in that individual is compared with the current knowledge about the meaning thereof. This creates a personal genomic database that can subsequently be used to deliver prevention, diagnostic testing and treatment to individual patients (personalised medicine). This should make it easier to help individual patients than is possible using current forms of care based on general epidemiological data. Furthermore, it would make healthcare more effective: less wasted means thanks to targeted interventions.

As with all major social futures, it remains to be seen what aspects of personalised medicine will be realised. A lot will depend on the degree to which 'genetic sensitivity' will allow useful risk and susceptibility profiles to be created for complex diseases (caused by interaction between genetic and environmental factors) and specific forms of therapy targeting such conditions.

## **1.2 Normative dimension**

Even if that future will initially be only partially realised, we are facing a development that raises ethical, legal and social questions that must be addressed in a timely manner. Given the scope of the potential social implications, the debate surrounding these issues is one that affects more than just the professionals involved.

The discussion in this monitoring report limits itself to the significance of the thousand-dollar genome to healthcare. This does not take away from the fact the debate deserves a broader approach. Sequencing and analysing the complete genome of individuals will also yield information that may provide insights into certain non-health related traits, such as behaviour, cognition and personality. The questions raised by this overlap those relating to information obtained about health. Both situations encompass sensitive data that could lead to stigmatisation and discrimination. Applications outside of the healthcare field also raise new questions, for example the advantages and disadvantages of using genetic information to provide differentiated treatment for children in terms of child-raising and education.

## **1.3 Structure of the report**

Chapter 2 outlines the backgrounds of the thousand-dollar genome. Chapters 3 through 7 discuss the potential applications thereof and potential related technologies (whole genome sequencing, whole genome analysis) within the context of medical diagnostic testing and for various forms of screening. These chapters will also identify the key normative questions raised. Chapter 8 contains an inventory of the potential consequences of the developments described for existing relevant frameworks. Chapter 9 ends with conclusions.

## **1.4 Justification**

The monitoring report was drawn up by Dr Wybo J. Dondorp and Prof Guido M.W.R. de Wert (Maastricht University, Research school CAPHRI) under the auspices of the Standing Committee on Medical Ethics and Health Law (see annex 1). A previous version was discussed with the Standing Committees on Medicine and Genetics. The research for this monitoring report partly took place within the framework of a project of the Centre for Society and Genomics (project nr. 70.1.070), part of the Netherlands Genomics Initiative.

## 2 Background

Whole genome sequencing is getting cheaper. This chapter provides a brief outline of the meaning the availability of this technology has for genome research and healthcare.

### 2.1 The hunt for the thousand-dollar genome

With the completion of a first, practically complete inventory of the human genome in 2003, a key goal of the Human Genome Project was reached, leading to the formulation of new challenges for further research.<sup>5</sup> In September 2005, the Graig Venter Science Foundation announced a 500,000 dollar prize for the first research group to manage to sequence an individual's entire genome for 1,000 dollars or less. The press release mentioned the major importance this breakthrough could have for healthcare:

Once this threshold has been reached it will be feasible for the majority of individuals to have their genome sequenced and encoded as part of their medical record.

The as-yet unclaimed prize has since been brought under the umbrella of the X-Prize Foundation. The prize money is now 10 million dollars. This will go to the first research group capable of sequencing the genome of 100 people with a high degree of reliability, within 10 days, for no more than 10,000 dollars per genome. The Foundation website links this objective with the promise of personalised medicine (targeted prevention, effective therapy, better vaccines, lower costs), but underlines that cheap, fast and reliable sequencing is primarily important for further research focused on unravelling the functional meaning of individual variations within the whole genome.

In addition to the cash prizes, a significant research grant from the National Institutes of Health (NIH) has led to strong competition between research groups and the development of numerous next generation sequencing techniques. Some of these techniques aim specifically to record individual genomes against the background of a known reference genome. This path appears to be leading the way to the thousand-dollar genome: in late 2009, researchers at the Californian company Complete Genomics announced they had successfully managed to sequence the entire genome for three people with a high degree of reliability for only about 5,000 dollars in consumables.<sup>6</sup>

The dropping costs of whole genome sequencing in the past years now allows the genomes of a larger number of people to be compared, allowing the genetic variation between people (and groups) to be defined further.<sup>7</sup> This research is initially focused on the protein-coding part of the genome (exome). This represents roughly one percent of the total, but is the part of the genome that appears to be most important for finding associations with disease risks.

## 2.2 Significance of the thousand-dollar genome for genome research

A subsequent step will allow researchers to further determine the potential meaning of variations for disease risks and other phenotypic differences between people. By comparing the genome of healthy people to that of sick people, the variations contributing to specific disease risks can be identified. This type of research is not new, but to date has only been conducted using information obtained through less detailed forms of whole genome scanning.<sup>8</sup> These studies primarily examine variation at the level of single base pair changes (single nucleotide polymorphisms, SNPs), small changes in the DNA that may be associated with an increased risk of common diseases.<sup>9</sup> Over ten million common (occurring in more than 1 percent of the population) SNPs have already been catalogued throughout the genome. Another approach (which can be combined with this one) looks at structural variations (insertions, deletions, copy-number variations: CNVs) within the whole genome.<sup>8,10</sup>

In only a few years, important discoveries have already been made by genome-wide association studies (GWAS) using these techniques.<sup>4,11</sup> However, not all (rare) disease-related variation can be tracked down this way. Once whole genome sequencing becomes affordable enough to be used for this purpose, it will likely provide a significant further impulse to this research.<sup>9</sup>

In order to clarify the contribution of genetic variation to the development of disease and differences in disease expression, more research is needed into the specific interaction between genetic and environmental factors, as well as into the insufficiently well-understood functional relationships between genetic factors (gene-gene interaction). One example is the study initiated in late 2009 in the United States into the as yet largely unknown genetic causes of autism.<sup>12</sup> To begin with, the exome (protein coding part of the genome) of all participants will be sequenced and analysed. The entire genome of participants this does not yield any results for will be sequenced. The researchers hope this will reveal regulatory genes in the non-coding part of the DNA that influence gene expression, thereby contributing to the development of autism. Without whole genome sequencing, the contribution of such genes is impossible to map systematically.



## 2.3 The thousand-dollar genome and the personalised medicine ideal

The expectations related to the availability of cheap whole genome sequencing dovetail nicely into attempts to personalise medicine. The most recently published Biotechnology Trend Analysis says the following on the subject:

The advantages of implementing the \$1000 genome are legion. Genetic screening or diagnostic testing will become cheaper over time. With increasing knowledge about the genome and the relationships between genes and the occurrence of a condition, in part thanks to the use of bio banks, screening via whole genome analysis may prove more valuable than the current per gene analyses. The possibilities for prevention and early treatment of diseases will increase, raising the average health level. The expected patient response to treatment and susceptibility to side-effects can be determined before treatment is begun, and new health promoting strategies will become possible. In short, the \$1000 dollar genome – and more generally X-omics research – allows for more tailored prevention and treatment of disease (personalised medicine).<sup>13</sup>

It is essential to note that the personalised medicine described can only be fully implemented in a 'proactive' model of healthcare, where one does not wait for people to exhibit disease symptoms, but health risks are mapped out while they are still healthy.<sup>4</sup> A health risk assessment to be carried out for everyone, recorded and kept up-to-date in an electronic patient file should allow various forms of information to come together in the form of risk profiles: questionnaire information about environmental factors and lifestyle, outcomes of psychological testing, family health history, findings of imaging tests and genomic information, both at a DNA level (stable genomics) and in terms of gene expression and protein and metabolic profiles (biomarkers).

The goal becomes the provision of preventive, diagnostic and therapeutic interventions across the entire continuum of health to sickness in a personalised manner based on the person's individual risk profile.<sup>4</sup> For healthy individuals: lifestyle recommendations and other forms of prevention; for people with health complaints: targeted diagnostic testing focussing on specific subtypes of conditions; for sick people: medication and other forms of therapy selected based on predicted response (personalised medication, pharmacogenetics).

Currently, only the first careful steps have been taken towards making this vision of the future a reality. In the past few years, important breakthroughs have been made in the implementation of genetic susceptibility profiles in the prognosis and differentiated treatment of cancer.<sup>4</sup> When it comes to the prevention of common diseases, the added value of genetic risk profiling remains largely hypothetical.<sup>14</sup> Although GWAS research has identified genetic risk factors for a number of common diseases, nowhere near all relevant risk increasing and decreasing factors for such conditions have been mapped out. Genetic susceptibility tests based on currently known variants are therefore not able to reliably differentiate between individuals who do or do not have a significantly greater or lower risk of disease. Offering such

testing is therefore premature.<sup>14-17</sup> Secondly, for most of the conditions in question (as shown in studies with identical twins), environmental factors have a far stronger influence on disease risk than genetic factors. The predictive value of genetic factor-based risk profiling will therefore only be minimal in most cases.<sup>18</sup> Only for conditions where genetic factors play a larger role in determining disease risk is this likely to be different. The promising results for a number of specific conditions (including age-related macular degeneration and Crohn's disease) fall into this category.<sup>14</sup> Thirdly: insofar as genetic risk profiling adds anything to prediction based on environmental factors, the clinical usefulness of the additional information depends on whether it will make the individuals involved more inclined to modify their lifestyle. This is far from certain.<sup>19</sup>

In summary, it remains extremely unclear if and when the promise of the personalised medicine ideal will be realised. The availability of the 'thousand-dollar genome': the ability to cheaply sequence complete genomes for individuals, is primarily important for the research into the complex relationship between genetic variation, environmental factors and health. Some commentators expect that in the future, this will lead to – as part of individualised health risk profiling – standardised whole genome sequencing and analysis for each individual. When speaking of whole genome analysis, this report always refers to the interpretation of the 'raw data' obtained by sequencing in the light of current knowledge on its meaning for the individual's health prospects.

The previously described scenario (routine analysis of the entire genome) is addressed in chapters 4 and 5 of this report. Chapter 3 will first examine a near-future application of the thousand-dollar genome in healthcare: whole genome sequencing with the goal of diagnosing disease for which the genetic background is not (or insufficiently well) understood.

## 3 Genome-wide diagnostic testing

Sequencing the whole genome is expected to play a role in healthcare in the short term, specifically in the diagnosis of diseases for which the genetic background is not or insufficiently understood. This chapter will first briefly outline the background of this application. Subsequently, a number of difficult questions raised by the fact genome-wide diagnostic testing inevitably means that far more genetic information about the patient is revealed than is necessary for answering the help demand, will be discussed.

### 3.1 Genetic diagnostic testing using arrays

Using micro arrays (DNA chips), it is currently already possible to perform directed analyses of selected sections of the patient's genome for diagnosis or prognosis based on relevant types of genetic variation (gene expression, structural variation and mutations of SNPs).<sup>20</sup> Such an array can, for example, be designed to specifically look for genetic factors known to play a role in the development of hereditary heart disease and the successful treatment thereof.<sup>21,22</sup> This kind of 'cardiochip' is expected to provide faster, more accurate diagnostic testing for patients with symptoms, a better test for tracking down asymptomatic carriers (early diagnosis, for example in athletes) and allow better justification of treatment strategies based on individual prognostic profiles.

Such a targeted approach is only possible if one knows in what part of the genome to look for the cause of the complaint or medical problem. This is not always the case. For example, the patient might be a child with a mental retardation with an unknown cause, or a patient with a rare neurological condition, unknown forms of cancer, and so on.<sup>23</sup> 'Genome-wide' arrays have recently been deployed for such cases, for example an array CGH which allows the entire genome to be searched for structural variations (such as gene deletions or duplications) that may explain the condition.<sup>24</sup> In 30 percent of cases in which an array was performed on the child, testing the parental genomes is also required to interpret the results.

### 3.2 Genetic diagnostic testing using whole genome sequencing

If costs are no longer a barrier, it is easy to imagine that every patient who requires genetic testing will undergo full genome (or to begin with the coding part of it: exome) sequencing. Whole genome sequencing (WGS) simply means making the entire genome accessible for

diagnostic analysis at a single base pair level. WGS provides 'raw data' (a library of three billion letter combinations) that means nothing without additional analysis. This analysis is conducted using software that reflects the (still limited) current understanding of the meaning of the variation found in the genome. Filters can be used to ensure as much as possible that only information relevant to the diagnosis of a specific health problem becomes available (targeted analysis). However, if it is unclear which genes need to be examined (for example in the previously noted situations in which genome-wide searches are already being conducted), a full analysis of the data obtained via WGS is the obvious choice: whole genome analysis (WGA).

### **3.3 Unsought for findings as a complication of genome-wide diagnostic testing**

Genome-wide diagnostic testing (currently still based on array technology, soon possible using WGS/WGA) does not look for specific abnormalities in certain parts of the genome in a targeted fashion, but searches the entire genome for the possible cause of an unexplained problem. It is inevitable that in addition to the sought information, unsought for information about known health risks will be revealed, as well as findings for which the meaning remains unclear. Currently, the latter by far applies to most findings of genome-wide diagnostic testing.

Unsought for, clinically relevant findings can have both positive and negative consequences for the parties involved (the examined individual, his or her parents, other blood relatives). If this concerns the predisposition for a condition that is preventable or treatable if detected in time, or information about carrier status of recessive conditions that affect (future) reproductive choices, the party involved will often see this as valuable new knowledge. This is likely also true for information on health risks that can be minimized through lifestyle changes. However, the situation is often different when it comes to, untreatable conditions. Such information can have negative social and psychological effects for the involved parties. This may include problems obtaining certain forms of insurance or getting or keeping jobs.

A number of recent publications have explicitly mentioned unsought for findings in genome-wide diagnostic testing and pointed out the challenge this presents for daily practice. The cases described related to genome-wide array CGH in children with unexplained mental retardation. In one case, a rare *de novo* (meaning: not inherited from the parents) gene deletion was found that leads to a very high risk of Li-Fraumeni syndrome.<sup>25</sup> This is a hereditary form of cancer which often occurs early in life, presenting with tumours in multiple organs. There is no effective treatment for Li-Fraumeni syndrome. In another case, carrier status for early onset Parkinsonism was detected.<sup>26</sup> Because the latter condition is recessive, this was not an additional disease burden for the child (other than a potentially higher risk of the late onset form of Parkinson's disease<sup>27</sup>). However, the finding did lead to further genetic testing of the parents due to their wish to have more children. There was a small, but not negligible chance that the father or the mother had two abnormal alleles of the gene in

question (Parkin). Such a result would predict that the parent in question would actually start developing symptoms of Parkinson's disease around the age of forty<sup>26</sup>.

Unsought for findings in diagnostic testing are nothing new in medicine (consider imaging techniques, for example). Targeted forms of diagnostic testing can also lead to unsought for information coming to light, potentially in relation to the disease or cause of disease that was the reason for initial testing. Genome-wide analysis does greatly increase the odds of such findings. It is already dubious to label findings of genome-wide diagnostic testing using current techniques as 'chance findings' or 'unexpected findings'; once all sequences within the genome are analysed, the position becomes essentially untenable. It is clear in advance that *all* genetic information available based on the current state of knowledge, health related and not, will be obtained, along with a large number of as yet not fully understood findings. All findings that are clinically relevant or otherwise potentially important to the parties involved will in principle have to be shared with them. Therefore, the consequences obtaining this information will have for the parties involved cannot be left unexamined, if such a far-reaching test is to be justified. That these findings are unsought, and therefore a 'by-product' of diagnostic testing performed on indication, is not a reason to view them differently.

In practice, attempts will be made to limit the problem of unsought for information by using targeted analysis (filters) wherever possible. However, if the location of the cause of the problem on the genome is unknown, a broad approach will be desirable. In theory, certain information considered undesirable can be filtered out, but the more filters, the greater the odds that testing does not lead to a diagnosis.

### **3.4 Informed consent and the right not to know**

Diagnostic testing and screening require the patient's informed consent. The care provider must give the patient the information he needs to make a personal and reasoned decision about the proposed treatment or testing. For genome-wide diagnostic testing, the fact the test may lead to unsought for findings must be discussed and the patient must be informed of the potential consequences. Only then can he or she (or the parents on behalf of their child) make a well-informed decision about the proposed tests. Do the health benefits associated with the test outweigh the odds of learning about damaging or otherwise disadvantageous health information? Particularly where whole genome analysis (WGA) is concerned, the question arises whether approaching the issue via the classic informed consent model is realistic. Can care providers themselves maintain a grasp of the potential outcomes of genome-wide diagnostic testing and the chances and implications thereof? Insofar as they can, do they have the time and the means to present this information to the person in question in an understandable fashion? Won't the amount and variety of the information, as well as the fact a great deal remains unclear or uncertain, preclude a well-informed choice?

The patient may wish to be informed about some unsought for findings, but not about all of them. For example, he might want to know about findings that indicate health risks that can be mitigated through timely treatment or lifestyle changes, but not about predispositions for severe conditions that cannot be treated or prevented. Recognition of both the right to know and the right not to know means that people should be given the opportunity to make such choices in advance.<sup>28</sup> Precisely how this should be given form is less clear. Discussing all possible findings in detail in terms of nature, severity and treatability is unrealistic. At most, a form of generic consent might be obtained<sup>29</sup>, where individuals can indicate the type of findings they do and do not wish to be informed of based on a number of general multiple choice questions. This approach is advocated in the previously mentioned publications on genome-wide array CGH in children with unexplained mental retardation. The authors propose asking patients, or parents of a child to be tested, prior to genome-wide diagnostic testing

whether (...) they wish to be informed about any additional genetic findings (without direct connection to the phenotype in question) with predictive value for the health of the proband and potentially her/his family; [whether] they only wish to be informed about such additional genetic findings if effective treatment options or surveillance programmes are available; [and also whether] they wish to be informed about a carrier status for an autosomal recessive disease – that is, about a condition which may have implications for reproductive decisions of the proband and/or family members.<sup>26</sup>

These formulations immediately raise a number of questions. To begin with, what the starting point should be: to inform or not? The authors appear to assume that clinically relevant additional findings unrelated to the initial problem should not be shared unless the party in question has indicated they do want to know. But isn't the opposite (yes, unless) also, and possibly even better defensible? Secondly, the choice about what the involved parties wish to know is limited to: 'findings (...) with predictive value for the health of the proband and (...) her/his family'. The final sentence, concerning carrier status for an autosomal recessive disease, can be seen as an exception to the limitation to health information. But is the limitation as such defensible? Should not the right to know encompass all genetic information that the involved party himself feels is useful, even if it does not apply to his health prospects? Thirdly: shouldn't the second sentence (addressing the delimitation of information that may contribute to actual health gains) not also address the importance of timely detection, the potential severity of the condition, and the stage of life in which initial symptoms may occur? Or does this immediately make everything too complicated, and does so much then need to be discussed and explained that little remains of the entire concept of generic consent? Fourthly, the question arises of whether doctors can fulfil their responsibilities for a child given into their care if parents pre-emptively indicate that they do not wish to know about additional, unsought findings of genome-wide diagnostic testing that may have significant effects on the child's health. Conversely, there is also the question of whether parents have the right to (health) information about their child that may only become relevant to him or her later in life.

Does this not rob the child (if it is not immediately clear that it will never be capable) of the possibility to later decide whether it wants to know or not know?<sup>28</sup> Finally, do formulations that refer to the interests of the child and of his or her relatives in a single breath not encompass too much potential conflict? Can the potential interests of relatives be a reason to limit the child's right to not know?

These questions emphasize that the notion of 'consent' (let the patient or his representative decide what he does and does not want to know) does not provide a simple solution to the complication of unsought for findings of genome-wide diagnostic testing, particularly where the interests of children are involved.

### **3.5 Inform or withhold?**

Clinically relevant information obtained through diagnostic testing must be shared with the patient (or his representatives), unless they have stated they do not wish to know. In principle, the same applies to unsought for findings that may be important for a patient's health prospects. This duty to inform is not absolute, however: under certain exceptional circumstances, the care provider may withhold health information because there is good reason for the worry that said information could severely harm the patient (therapeutic exception). The implementation of genome-wide diagnostic testing may lead to situations that raise such issues. Should the finding – unrelated to the original testing reason – that a girl runs a very high risk of developing breast cancer be shared? For minors, in addition to potential harm (psychosocial, social) it is also important to remember that sharing such information may violate future autonomy, unless of course there is such a severe mental handicap that it is clear the child will never be capable of making autonomous choices. The prevailing consensus in the debate on predictive testing of children for severe late onset diseases remains that such testing is not permitted unless treatment or prevention that must be initiated during childhood is possible.<sup>30</sup> What does this entail for the acceptability of sharing unsought for information with the same implications? Does it make a difference that the information is already available? Furthermore, the information may also be of great importance to parents or other blood relatives, either in terms of their own health prospective, or in relation to reproductive choices. Imagine genome-wide diagnostic testing reveals a child runs a very high risk of developing hereditary breast cancer later in life. The information is not relevant to her at this time, and only has the potential to be harmful. Is withholding the information until adulthood a realistic option? Does the right of the child to not yet know prevail of the current importance for the health of mother and aunts?

In addition to desired and unsought for information, genome-wide diagnostic testing mostly yields data for which the clinical significance is as yet unclear. What can be considered useful information, and what part of it is noise to be withheld? The scientific research mentioned in the previous chapter will lead to fleshing out more and more knowledge gaps in the years to come. Part of what is currently noise will prove to be meaningful information.

### 3.6 Storage of genetic data

Another issue is what should happen with all of the (largely unsought) information generated by the implementation of whole genome sequencing and analysis in clinical genetic practice. A differentiation must be made between the raw data which is the product of sequencing (WGS) and the outcomes of the sequencing analysis (WGA).

The raw data can be stored (in the patient file) for future analysis. Should additional genetic testing be necessary later in the patient's life, the data will not need to be generated again. This assumes the costs of storing the data do not outweigh those of new sequencing, and that newer sequencing will not be more sensitive or better than current techniques. Costs include not only the permanent physical storage of the data, but also securing it. Although the raw data obtained through sequencing has no meaning, anyone with the correct software can theoretically perform the analysis. Therefore, the raw data must also be considered and treated as privacy-sensitive data.

Genetic data obtained through sequence analysis will need to be stored in the patient file, at least insofar as data relevant to the patient's (or their relatives') health prospects are concerned. This raises the question of what should happen with genetic information that has been obtained, but is not desired by the patient and has therefore not been shared with him. How can this information be stored in such a way that the patient is not unwittingly confronted with it? Is it not better to destroy said information? Is this allowed, or perhaps even mandatory? Can this problem be solved by asking the patient in question what should happen with data he or she does not wish to know about during pre-test counselling? What about data obtained about a child that may be important in his or her later life (including reproductive decisions)? Another question is what should happen with findings with unclear meanings, or that do not appear relevant for health prospects. Do they belong in the medical file, as the future may tell whether they do have health-related relevance? Undoubtedly, the implementation of genome-wide diagnostic testing will lead to new debate about how long data must be stored in the medical file.<sup>31</sup>

### 3.7 The thousand-dollar genome and the role of the doctor

Within the field of medicine, the debate is ongoing regarding the extent to which doctors can be expected to contact patients treated (or counselled) in the past if new scientific insights make improved diagnostic testing or prognostics possible for the condition the patient was treated for.<sup>32,33</sup> On the one hand, it seems only natural to do so if the involved party may expect health gains, or at the very least greater insight into his medical condition. After all, wasn't that the original reason for seeking out medical aid? On the other hand, it is uncertain that the party in question actually wants to receive the new information, with all that implies, even if it might potentially lead to health gains. Where legally incompetent people are concerned, the question arises whether renewed contact is truly in the best interest of the



party in question. Hunter et al.'s warning appears justified: 'the uninvited recontacting of patients includes significant risk of causing harm'.<sup>33</sup>

The legal aspects are also far from simple. As long as there is an ongoing doctor-patient relationship (this applies to the GP, but possibly also to specialists if there are regular check-ups), there is a clear framework within which the doctor may be expected to inform the patient about new, relevant insights (wherever possible taking into account his or her explicit desire not to receive certain types of information). But does this responsibility extend beyond that? To what degree is it part of the aftercare that may be expected of a good care provider? And is it only about gaining new insights within the context of the original request for help, or does this responsibility also extend to other aspects of health?

The introduction of genome-wide diagnostic testing makes these questions all the more urgent. New scientific insights into the meaning of certain genome sequences may cause test results recorded in a patient's medical file to be viewed in a new light. Data that initially appeared not to have any clinical relevance are suddenly important to the patient's health. Can part of the problem be removed by asking patients when entering into a treatment relationship whether and under what conditions they would like to be contacted again if new scientific insights warrant it after the end of said relationship? This is also not without problems: 'this does not take account of the matter that the patient cannot foresee the future and the possible impact that new information could have, or that their perspective may change with time'.<sup>33</sup> Furthermore, there is the question of what active and systematic implementation of a broadly implemented duty to recontact would entail for the burden placed on care providers and the organisation of healthcare. Would it not be preferable, so some have proposed, to advise patients to take the initiative after a few years to ask whether new knowledge has been obtained that may be relevant to them?

The above concerns recontacting after termination of the treatment relationship. However, this does not answer the question within the context of an existing doctor-patient relationship: what do all the unsought for and non-care question related outcomes of whole genome analysis mean for the scope of a doctor's responsibility? This is also not an entirely new question. The previous monitoring report from the Centre of Ethics & Health (CEG) on screening in general practice pointed towards a possible shift in the GP's/doctor's task conception: from a solely complaint-oriented care provider to a 'health monitor' who also advises patients on all possible aspects of health on his own initiative.<sup>34</sup> The introduction of the thousand-dollar genome raises the same questions about the role of the doctor and the nature of the doctor-patient relationship. If the medical file contains all of the results of whole genome sequencing and analysis (performed within the context of medical diagnostic testing), is it up to the doctor to inform the patient if new knowledge is obtained about the health implications of that data, even if it has nothing to do with the original reason for the test? And how should cooperation be organised and responsibilities be shared between GPs and specialists?



## 4 Genome-wide screening of adults

The thousand-dollar genome not only opens possibilities for diagnostic testing, it also brings genome-wide screening closer to becoming a reality. Some advocates of the personalised medicine ideal believe it would be wise to analyse the genome of every individual in a systematic and active manner. After all, this data is an important precondition for preventative and curative medicine tailored to personal health needs. As this would entail (systematically) offering (genome-wide) medical testing without a cause in the form of complaints or a family history of disease, this is not diagnostic testing, but screening.<sup>16,35</sup> This chapter discusses the implication of genome-wide screening of adults.

### 4.1 Genome-wide screening and use of filters

As is the case within the context of diagnostic testing, the distinction between sequencing and analysis is also important here. Sequencing the entire genome (WGS) may, but need not mean that all raw data are also analysed (WGA). Using filters allows partial analysis to be performed: this technique examines certain parts of the genome while leaving the rest of the raw data unanalysed. After full or partial analysis, the raw data (the sequenced genome) can remain available for further analysis should it be necessary at any point in the future. If sequencing were to become so cheap in the future that careful storage of the data is more expensive than generating it anew, it is likely the data will be destroyed after each use.

Use of filters allows the implementation of whole genome sequencing as the basis for targeted genetic screening. If screening for a specific disease or susceptibility requires searching for multiple mutations, sequencing the entire genome may prove to be a cheaper solution than using individual tests. Filters can be used to prevent uncovering unsought information wherever possible. The fact this is not always possible is no different from current forms of targeted genetic screening. How these filters should be fine-tuned in daily practice (for both diagnostic testing and screening) will remain a complex issue: a test with a broader scope may be more informative, but may also yield more difficult to deal with unsought information.

For genome-wide screening with the purpose of analysing personal genomes, it is imaginable that filters will be used to filter out certain predictive information not wanted by the party in question. This could include predispositions for untreatable late onset diseases, genetic

sensitivity to psychiatric conditions, or other outcomes that may represent a major burden and could have negative social consequences.

## 4.2 Analysing the personal genome

As a proof of principle, American physicians and researchers recently published about sequencing and analysing the 'personal genome' of a 40 year-old man. He had a family history of cardiovascular disease and early sudden death, but no complaints of symptoms himself.<sup>36</sup> The analysis focussed on clinically relevant genetic variation: predispositions for monogenetic diseases, lesser or greater genetic sensitivity to common conditions and variants that influence individual response to medication. The outcomes included rare variants in genes associated with sudden cardiac death and an increased sensitivity to having a heart attack (no surprise, given the family history), but also gene mutations associated with diseases not present in the past history, carrier status for recessive conditions, pharmacogenetic information and information about greater or lesser odds of common diseases, with higher post-test scores for conditions including cardiovascular disease, obesity and type 2 diabetes. The goal of the exercise was to demonstrate analysing personal genomes can yield clinically relevant information.<sup>36</sup>

In the (currently hypothetical) scenario in which the ideal of personalised medicine is so well developed that analysing personal genomes could make a valuable contribution to individual personal health management, the question of optimal timing arises. The earlier the information is obtained, the greater its potential value for the individual and for healthcare. Two possible points in time are mentioned in the debate: as early in life as possible, meaning at birth (see Chapter 5 for more) or upon reaching legal age.<sup>37,38</sup> In the latter case, the individual can decide for himself whether or not to take part in this form of screening, while it is still early enough in life for potential benefits to be significant. Potential benefits not only include using the obtained information for personalised lifestyle recommendations, prevention and interventions during the course of the individual's life, but also the potential value of the information for the reproductive decisions that many young adults will have to make.

In addition to the potential advantages of analysing personal genomes, there are also all too real disadvantages to obtaining information that could be a burden or even harmful. Here too, filters could be used to decrease the odds of obtaining unwanted information. What does need to be considered is that the exact meaning of genetic variation is currently largely unknown and that the use of filters is based on current levels of knowledge. What appears to be innocent noise now, may prove to be meaningful later. Disadvantages also include worry caused by (still) unclear outcomes, as well as the subsequent – often unnecessary – contacts with healthcare (counselling, further testing, treatment). As long as there is no clear positive balance of advantages and disadvantages, there can be no responsible implementation of genome-wide population screening within public health care (see 8.3). However, it is likely commercial providers will see a market for this kind of testing before then. In effect, the market

already exists, albeit currently only implementing less advanced (and therefore much cheaper) tests that only examine small, common variations in the genome.

In his recent book *The Language of Life*, Francis Collins (director of the American National Institutes of Health, former director of the National Human Genome Research Institute) describes his experience with such tests. Collins had his genome tested by three different commercial outfits: *deCODE*, *23andMe*, *Navigenics*. The laboratory tests he received in return (after submitting physical samples) were largely the same, but the interpretations included (in terms of higher or lower risk of developing certain common conditions, or a greater or lesser sensitivity to certain commonly used medicines) displayed differences reflecting the 'immature state of making predictions from these DNA results'.<sup>39</sup>

However, Collins does believe these are the beginnings of a positive revolution in how we address health: 'learning your DNA secrets can be the best strategy for protecting your health and your life'.<sup>39</sup> People who know (like Collins) that they have a slightly elevated risk of type 2 diabetes will be more motivated to listen to lifestyle recommendations or exercise more, for example. Whether this actually works (and if so, under what circumstances, and for whom) is a question that requires further research to answer.<sup>19</sup> Regardless, according to Collins, fully sequencing and analysing personal genomes will be the next step in the development, and one we can expect soon:

The analysis I had done tested one million places in my DNA. But this is just the beginning. Soon, probably within the next five or seven years, each of us will have the opportunity to have our complete DNA sequenced, all the three billion letters of the code, at a cost of less than \$1,000. This information will be very complex and powerful. Careful analysis of the complete content of your genome will allow a considerably more useful estimate of your future risks of illness than is currently possible, enabling a personalized plan of preventive medicine to be established.<sup>39</sup>

### 4.3 Preconception carrier status screening

In the scenario outlined by Collins, it would be wise not to wait until middle age has passed (as it had in his case) to have one's personal genome analysed. Not only because personal prevention is best initiated early, but also because in addition to information that can affect one's own health, information will also be obtained about diseases not affecting oneself personally, but that may be passed down to offspring. This relates to (sex linked or autosomal) recessively inherited disorders. Most people who are (healthy) carriers of such diseases are not aware of it, so having a child with the disorder in question comes as a complete surprise. Autosomal recessive conditions only lead to disease if both man and woman are carriers of the condition. In such cases, the odds of having a child with the disease are 1 in 4. People who know this in advance can take this into account when making reproductive choices. In addition to deciding not to have (genetically related) children, options include prenatal diagnostic testing with the possibility of abortion if the foetus has inherited the disease gene

from both parents, or reproduction via in vitro fertilisation (IVF) combined with embryo selection (PGD) focused on ensuring any children born do not have the disease.

Of course, it is unnecessary to analyse the entire genome in order to test for carrier status for recessive, inherited diseases. At this point in time, it is far more logical to implement targeted preconception carrier status screening for relevant mutations.<sup>40-42</sup> The Health Council of the Netherlands, among others, has recommended examining whether such screening can be offered to people of reproductive age. This screening should allow tracking down or ruling out carrier status in the population for common autosomal recessive diseases such as cystic fibrosis and haemoglobinopathies.<sup>42,43</sup> New techniques, such as the use of DNA chips and sequencing, will allow carrier status to be determined for many more recessive conditions than have been the topic of discussion in our country until now, without significantly increasing the costs. A Californian company recently introduced a 'universal' (meaning: not only suitable for a subpopulation) carrier status test which can identify carrier status for over one hundred rare, recessively inherited conditions using a single test.<sup>44</sup> An individual test costs 350 dollars, and is (partially) covered by some American health insurance companies.

Critics have pointed out that it remains to be seen how reliable the test is in identifying all of these conditions.<sup>45</sup> False positive results may cause unnecessary worry and testing, along with the associated burden, risks and costs thereof, as well as lead to unnecessary decisions not to reproduce or have a genetically related child. Furthermore, the message that this is a 'universal test' could easily lead to the misconception that normal results guarantee healthy children. The fact there are many more rare, recessive conditions than the hundred targeted by this test alone means one should be wary of unwarranted reassurance. However, this does not invalidate the usefulness of a broad, preconception carrier status test, as long as it is of good quality and offered in a well thought-out manner.

#### **4.4 From a genome-wide test for carrier status risks to a personal genome?**

It can also be expected that the offerings of the company mentioned above is only a first step towards further expansion. At a poster presented during the conference of the American Society of Human Genetics in November 2010, American researchers from the National Center for Genome Resources announced they were working on a next generation sequencing-based test for carrier status for more than four hundred recessive, inherited conditions, to be offered to couples wanting to have children.<sup>46</sup> Individuals wanting to compare their full risk of transmitting recessive conditions to a potentially corresponding risk profile in their partner will ultimately not be satisfied with anything less than mutation analysis of the entire genome. In his above-mentioned book, Collins writes:

Debates about the appropriateness of carrier screening will be likely to change in the coming few years, as more and more individuals will have complete DNA sequences of their entire genome determined, revealing all of their carrier status risks and providing an opportunity for couples to

know about those risks prior to initiating a pregnancy. It is likely that within a few decades people will look back on our current circumstances with disbelief that we screened for so few conditions.<sup>39</sup>

If whole genome sequencing becomes a cheap, and therefore obvious choice for charting 'all carrier status risks' in the near future, this means filters will be required to limit the analysis to these carrier risks. However, in the scenario described by Collins, the question arises of why one would do this. The filters need only be left out to move from a genome-wide carrier status test to analysing the entire genome. On a content level, this is a major step with far-reaching consequences, due to the far greater complexity of the genetic information that will be obtained. Not everyone is as convinced as Collins that analysing entire genomes will be of overall benefit to the individuals involved or to society. As long as the advantages are uncertain, and the potential disadvantages loom large, it appears wise not to take this step. However, if the only thing necessary to implement it is removing filters, the debate on the advantages and disadvantages of personal genomes is placed in a new light. The question then becomes not what we *do* want to know about ourselves, but what we *do not*.





## 5 Genome-wide screening of newborns

In the debate on the contribution personal genomes may make to the ideal of personalised medicine, there are also voices calling for analysing the personal genomes of newborns. In addition to the questions raised in the previous chapter, this also leads to a new potential problem: how does this relate to the right to self-determination?

### 5.1 Genome-wide screening of newborns: a good idea?

Some commentators believe it is wise to sequence and analyse an individual's entire genome at the very beginning of his life, as part of the existing heel prick screening of newborns. This makes genetic information available from birth that can be used to deliver personalised disease prevention and health promotion initiatives. A British government report presented the idea as follows:

One long term possibility that has been suggested is to screen babies at birth as part of the standard postnatal checks and to produce a comprehensive map of their key genetic markers, or even their entire genome. Major investment is currently being made in information technology in the NHS [National Health Service], including the development of an electronic patient record for each person. The baby's genetic information could be securely stored on their electronic patient record for future use. It could then be used throughout their lifetime to tailor prevention and treatment regimes to their needs as further knowledge becomes available about how our genes affect our risk of disease and our response to medicines.<sup>47</sup>

According to the previously referenced book by Collins, it is 'almost certain' that complete sequencing will become part of neonatal screening in the next few years:

(...) as we learn more about effective interventions for genetic risk factors, and recognize that interventions early in life provide significant advantages, it will become more and more compelling to determine this information at birth.<sup>39</sup>

Upon request of the British government, the Human Genetics Commission has examined this idea. In its report (*Profiling the newborn: A prospective gene technology?*) the committee concludes to reject the idea. No matter the exact balance of advantages and disadvantages – depending largely on the realisation of the ideal of personalised medicine – analysing a

newborn's complete genome violates the principle of respecting autonomy.<sup>38</sup> After all, such screening will reveal all kinds of findings that are of no importance to the child's immediate health, but may have serious consequences for his or her later life. By actively looking for such information unasked, the child may not only be harmed, but he or she will also be robbed of the choice to decide for him/herself, later in life, as an adult, about what he/she wants to know about his or her genome.

That the child cannot consent to being tested does not stand in the way of current heel prick screening, because it is focussed on treatable conditions of early childhood. Analysing the entire genome, however, will inevitably lead to obtaining predictive information about potential health problems that are only expected later in life. This may include information about an increased genetic sensitivity to common (multifactorial) diseases (such as diabetes or cardiovascular disease). But it can also reveal carrier status for monogenetic abnormalities that can lead to disease later in life, including severe conditions such as hereditary breast or ovarian cancer, Huntington's disease, or the hereditary form of Alzheimer's disease. The prospect of developing such a disease (or awareness of a high risk of doing so) is a burden that could harm the child's psychosocial development. Furthermore, this information, which cannot always be concealed, could lead to difficulties obtaining some insurance cover and potentially to discrimination in the employment market.

There is a broadly shared (but not universal) consensus that children may not be tested for carrier status of diseases that only manifest in adults, unless there are treatment options or forms of prevention that must be initiated in childhood in order to significantly change the course of the disease.<sup>28,30,38</sup> In the absence of such interventions, the child will primarily experience the negative effects of a positive (unfavourable) test result. Furthermore: once the information is out there, he or she can no longer choose whether or not to know later in life. This violates what Feinberg calls the child's anticipatory autonomy rights.<sup>48</sup> The child cannot exercise his or her right to self-determination yet, but others can still make decisions now that retain or violate his or her future rights. Within this context, Feinberg refers to the child's right to 'an open future'.

Criticism of this approach has come from authors who emphasize it can also be in the child's best interest to grow up being fully aware of carrier status of severe late onset conditions.<sup>49</sup> By emphasizing this aspect, they put the autonomy argument into perspective. Most authors do not support this viewpoint. Regardless, this debate relates to genetic screening requested by worried parents from families with a history of disease. This is a completely different context from screening, in which the party in question may obtain unexpected information about severe late onset conditions.

It must also be considered that the information available through genome-wide analysis not only affects the child's (future) health, but also all manner of other traits partially affected by genetic factors, such as behaviour, personality and cognition.<sup>39,50</sup> These are all extremely

complex properties for which little is currently known about the genetic component. The danger exists that incomplete knowledge about potentially relevant genetic characteristics will still be used by parents when making child-raising choices. The question remains whether this is in the child's best interest. A very real worry is that overvaluation of the genetic factor will pre-emptively limit the child's room to develop differently from how parents fear or wish. The 'right to an open future' is endangered here as well. In the meanwhile, commercial parties are already addressing potential interest in parents. For example, the website 'mygenes-mychild' advertises testing children for genes that could play a role in the development of behavioural problems without second thought:

Obtaining a child's genetic information through genetic testing can possibly help parents know what to expect. The gene variant that scientists look for is the one that allows children to learn from their mistakes. About 30 percent of people lack that capability, genomic scientists now say. This information can prepare you to raise your child.\*

The idea of holding back certain information (not to share it with the parents but store it nonetheless) until such time as the child is capable of deciding what he or she does or does not want to know<sup>39</sup> does not solve the problem. How to prevent the child receiving the information without wanting to? And is it possible to enable the child to do something with the information without impinging on his or her right to not know? It appears more useful to pre-emptively use filters to prevent information from becoming available that has no advantages for the child but does have potential disadvantages, and that also rob him or her of the possibility to later decide what he or she wants to know about his or her personal genetic makeup. This does raise the question of what then remains of the concept of analysing the entire genome at birth. If the filters are applied strictly, this will result in a form of screening with a scope that does not differ significantly from the current heel prick.

## 5.2 Genome-wide screening of newborns: an inevitable development?

The American President's Council on Bioethics (PCBE) has noted an irresistible trend towards increasingly broad screening of newborns.<sup>51</sup> The PCBE is no less critical of such practices than the British report referenced above, with the important difference that they do not see genome-wide neonatal screening as a hypothetical scenario, but as an inevitable endpoint of an ongoing development that is being guided by a number of factors that strengthen each other. The logic of personalised medicine is primary among these:

Once personalized genomic medicine becomes standard medical practice for adults, the logic of providing physicians with this powerful tool earlier and earlier in the patient's life may prove inescapable. Even if cancers, for example, are relatively rare in children and adolescents, why wait until adulthood to uncover susceptibilities and vulnerabilities that could well be countered by changes in diet and life habits (to say nothing of prophylactic therapies) at an early age?<sup>51</sup>

\* <http://www.mygenes-mychild.com/articles/childs-genetic-information/index.php>

The PCBE sees the further development of the research importance of this concept (personalised medicine) as a second factor driving broadening of neonatal screening:

An obscure illness for which there is as yet no treatment is more likely to be elucidated and ameliorated or cured if newborn screening gives the medical community an accurate picture of the prevalence of the disorder as well as early access to as many of its sufferers as possible.<sup>51</sup>

The American National Institute of Child Health and Human Development (NICHD) is already investing in this approach and is 'expanding screening technologies and developing effective therapies as concomitant activities'.<sup>52</sup> This has contributed to some researchers pleading for replacement of current neonatal screening tests (particularly tandem mass spectrometry, a technology not based on genotype, but on concentration of substances in the blood) with screening using DNA chips.<sup>53</sup> The NICHD is considering step-wise expansion of neonatal screening to include conditions with known mutations for which experimental, innovative therapies are being developed. In principle, all clinically relevant genetic abnormalities, including those that only lead to disease later in life, qualify for inclusion in the test panel:

The technology could be expanded to screen for additional disorders as mutational analysis or other multiplex technology become available, with decisions being based more on what not to screen for (perhaps Huntington's disease) than on what to include.<sup>52</sup>

If genomic medicine and the technological capacity to realise it. This agenda demands screening that is as broad as possible. The authors acknowledge that all manner of other abnormalities will be found with uncertain health implications for the child. However, they emphasize, the goal is to broaden knowledge about these findings: 'as our understanding of the function of the DNA sequences increases, we should see an increase in the accuracy and predictive power of the tests'.<sup>52</sup>

As soon as affordable whole genome sequencing allows analysing the entire genome for all newborns, this would appear to be the next logical step in this research-driven approach. After all, testing for pre-selected genetic abnormalities alone is not enough to fully understand the relationship between genotype and phenotype. Whole genome analysis allows research to start from the other end of the spectrum and track relevant risk increasing or decreasing factors in unexpected parts of the genome. This is expected to generate a better understanding of both common and rare conditions, enabling better, personalised treatments to be developed. This requires large-scale research databases (bio banks) that can be used to examine associations between specific genotypes and health data from individuals in various phases of their lives, starting at birth or even before.<sup>51,54</sup>

Finally, the PCBE notes there is social pressure from parent organisations of affected children as well as consumer organisations in healthcare to broaden the scope of the current heel prick screening. The debate in our country (see 5.3) is currently focussed on screening for

conditions that manifest shortly after birth or in childhood, not on analysing the whole genome. According to the PCBE, however, there is broad support among the American public for the idea that parents simply have the right to all available genetic information about their child.<sup>51</sup> The outcomes of a recent American study among a large group of parents with underage children support this assertion. A full third of respondents said they would be interested in genetically testing their youngest child for severe, untreatable late onset conditions.<sup>55</sup> The authors correlate the findings with penetration of the message broadcast by commercial parties that genetic testing is an issue of 'rightful ownership of one's personal health data'.

The fact the data belongs to the child – that it's someone else's data – is a distinction these companies prefer not to address in their marketing strategies. Instead, they appeal to the parents' sense of responsibility. The implication is that parents not only have the right, but also the moral duty to obtain information about the genetic makeup of their children:

What to eat, what to avoid, what to talk to your doctor about – think what you may have done differently with access to your genetic information when you were younger. Having your child take a genetic test at an early age can help him or her lead a long and healthy life, making informed decisions about their health.\*

The PCBE emphasises that these three factors: the logic of the concept of personalised medicine, the research importance that results from the development of said concept, and the broad support among the American public for the idea that parents have the right to know as much as possible about their children's health prospects potentiate each other to such a degree that 'it may, in fact, prove impossible to hinder the logic of genomic medicine from assimilating the currently limited practice of newborn screening to its all-embracing paradigm'.<sup>51</sup>

### 5.3 Expansion of neonatal screening: what are the limits?

In The Netherlands, current heel prick screening focuses solely on conditions where timely treatment or prevention (often a diet) can prevent significant health harm to the child.<sup>56</sup> This is consistent with the traditional principle that screening of newborns can only be justified if the child may expect to benefit directly.<sup>57</sup> However, this principle is also under pressure in our country. There have been voices advocating screening for untreatable conditions of early childhood for some time. This could not only make it easier to understand early symptoms (avoiding a stressful medical hunt for a diagnosis and allowing immediate adequate care to be provided), but also provide important information to parents who wish to have more children.<sup>58</sup> If they know their child has a severe hereditary condition, they can take the odds of it occurring again (usually 1 in 4) into account when making future reproductive choices. The debate on this subject is ongoing, but support appears to be growing for the position that neonatal screening for untreatable conditions that (also) benefits parents or the family as a whole is not

\* <http://www.mygenes-mychild.com/articles/childs-genetic-information/index.php>

per definition unacceptable, as long as the child itself does not suffer any negative consequences thereof.<sup>16,59</sup>

The latter implies that potential broadening of screening would solely encompass conditions of early childhood. Further broadening of the scope could easily harm the child's right to autonomy. At this time, the limit (diseases of early childhood) does not appear threatened in our country. However, current technology (tandem mass spectrometry) does not allow further broadening of the scope. In the meantime, DNA chips can track down diseases that meet current criteria, but cannot be identified using current technology.\* The question remains what will happen when the switch is made to test based on genome-wide screening for technical or financial reasons.<sup>53,60</sup> Adhering to the principle that only (treatable) conditions of early childhood may be screened for, this means filters will need to be used during analysis to prevent information about the whole genome from becoming available. Once again, the question becomes not what *should* be tested for, but rather what *should not*. Whether public opinion will be immune to the belief that parents have the right to all possible information that such a genome-wide test can provide about their child, remains to be seen. Even the current limitation to severe but treatable conditions has been criticised as a violation of the right of parents to 'decide for themselves whether they want to have their child screened for more conditions'.<sup>61,62</sup> All told, it is not unthinkable that pressure will increase to move beyond the boundaries of early childhood diseases in the future.

\* Professor RA Wevers, University Medical Centre Nijmegen, personal message

## 6 Genome-wide prenatal diagnostic testing and screening

It is easy to imagine the thousand-dollar genome affecting genetic testing during pregnancy. This chapter addresses the dynamics of current developments in the field of prenatal diagnostic testing and screening. There is also a tendency towards increasingly broad scope testing.

### 6.1 Genome-wide prenatal diagnostic testing

Genome-wide (array CGH based) tests are already used in prenatal diagnostic testing, specifically to help assess unclear findings during structural ultrasound imaging (20-week ultrasound). This form of diagnostic testing requires obtaining cell materials via amniocentesis. The goal is comparable to that of postnatal use of genome-wide diagnostic testing to elucidate the genetic background of unexplained mental retardation or other abnormalities for which it is unclear where precisely the genetic cause needs to be looked for, as described in chapter 3. Prenatal diagnostic testing of this type is more difficult, because there is no way to determine the child's phenotype. It is conceivable whole sequence analysis will eventually also be used in this field. The context is different, however. The structural ultrasound imaging is performed at gestation period of about 20 weeks. This is a screening ultrasound offered to all pregnant women, during which all kinds of structural abnormalities may be seen, as well as some abnormal findings for which the exact meaning remains unclear. The goal of this ultrasound includes providing the pregnant woman with additional information that she may use to determine whether to carry the pregnancy to term or terminate it.<sup>41,63</sup> Implementation of genome-wide diagnostic testing to help interpret unclear findings during the 20-week ultrasound allows the pregnant woman to be better informed about the potential nature and severity of any condition or handicap in her unborn child. At the same time, it is clear such testing can also yield outcomes that make the decision facing the pregnant woman (or couple) even more difficult, for example if the condition found is mild, or only sometimes – but nowhere near always – leads to severe symptoms.

Genome-wide (array CGH based) diagnostic testing is also used for a specific outcome of screening for Down syndrome, a significantly thickened neck fold (> 3 or 3.5 mm). This screening outcome must take into account a broad spectrum of potential sub microscopic chromosomal abnormalities that can lead to extremely severe conditions.<sup>64</sup> Here too, the objective is to provide the pregnant woman (and her partner) with the best possible

information about potential foetal abnormalities, allowing a well-considered decision to be made about whether or not to continue the pregnancy. If the decision is made to carry the pregnancy to term, obstetric and perinatal care can be offered based on the outcomes of the diagnostic testing in order to provide the child with optimal support.

## 6.2 Genome-wide prenatal screening

In the meantime, the use of array CGH is being discussed as an alternative to current microscopic chromosome testing (karyotyping) for pregnant women who have undergone chorion villus sampling or amniocentesis solely due to an elevated risk of Down syndrome or other trisomic conditions.<sup>65</sup> This is different from the situation described above (clarifying outcomes of the 20-week ultrasound, significantly thickened neck fold) as there is no indication for broader screening in this group. The elevated risk of Down syndrome or other trisomic conditions is an indication for diagnostic testing of the chromosomes in question, but does not (unless a significantly thickened neck fold is present) require testing for other chromosomal or genetic conditions. When viewed in this context, the current karyotyping method already has a broader scope than necessary, which recently lead to the proposal to replace it with a more targeted test looking only at trisomy 21 and a few other forms of aneuploidy.<sup>65-67</sup>

If other parties<sup>68-70</sup> then propose a broader test, this is essentially a plea for additional prenatal screening\*, to be offered to women who already qualify for a (expensive and not entirely risk-free) chorion villus sampling or amniocentesis due to an elevated risk of having a child with Down syndrome. In the United States, where women without an elevated risk of having a child with Down syndrome (or a specific indication for prenatal diagnostic testing) who want to be tested can undergo a chorion villus sampling or amniocentesis<sup>71</sup>, this type of array screening could become available to all pregnant women (who can afford it). This is already the case in a few select centres. In a plea to broaden the scope of prenatal screening, American geneticist Beaudet justified it as follows:

If we are committed to offer prenatal diagnosis for Down syndrome, we should be prepared to offer it for other disorders of similar or more severe disability unless the risks or costs are prohibitive.<sup>72</sup>

As long as invasive procedures (chorion villus sampling, amniocentesis) are required to obtain the foetal testing material, the associated costs and the risk of miscarriage will present an important limiting factor. Although important steps are being made towards developing non-invasive pre-natal testing methods using foetal DNA in maternal blood (NIPD: non-invasive prenatal diagnosis<sup>73,74</sup>), the question remains whether the technology will be usable for genome-wide screening or diagnostic testing. Should this be the case, it will become possible

\* The test is itself diagnostic; nevertheless, as this would relate to a routine offering without specific medical indication, it would constitute offering a test for screening purposes (GR 1994, 2001).



to offer genome-wide prenatal tests to all pregnant women at an early stage of the pregnancy as a risk-free one-step screening.<sup>75,76</sup>

Practically no research has been done to determine whether pregnant women would want such a genome-wide test. In an American study, pregnant women who (for various reasons) qualified for an amniocentesis or chorion villus sampling were given the option of having an array CGH test performed in addition to the standard karyotyping for no additional cost. 33 of the 45 pregnant women agreed to the offer. The most commonly listed reason was the desire to obtain as much information about the foetus as possible. The women who rejected the test did so because they were afraid of additional worries, and because they felt the additional conditions that might be found were extremely rare.<sup>68,77,78</sup> Of course, array CGH is not the same thing as a full sequence analysis, but as soon as the costs of whole genome sequencing no longer present a barrier, it is not unlikely that further expansion in that direction will be advocated. Those who want to obtain (and to provide) 'as much information as possible about the foetus' will eventually no longer be happy with anything less than the complete genome.

### **6.3 Practical courses of action: the more choice, the better?**

The goal of prenatal screening for foetal abnormalities was defined as follows by the Health Council: to enable pregnant women (and their partners) to become aware of the potential presence of the condition in question in the foetus, and to use such knowledge to make an informed decision about whether or not to carry the pregnancy to term.<sup>63</sup> The justification of the screening offerings lies in providing reproductive choices (practical courses of action) that would otherwise not be available to the parties involved. What remains unanswered is the question of how broad the scope of these offering should be.<sup>67</sup> The developments discussed above mean debate on this subject in the near future is inevitable. What conditions should prenatal screening be offered for, and who gets to decide? Does the goal of promoting reproductive autonomy imply the pregnant woman should have the greatest possible number of choices and thus – if she states she wants them – should be informed about as many other conditions the foetus may have as possible in addition to the presence of Down syndrome? Or does this lead to her having to process too much information, making a well-informed decision about how to continue the pregnancy more difficult rather than easier?<sup>79</sup>

The broader the test, the more diverse the potential outcomes, the more difficult it will be to enable the pregnant woman to provide true informed consent. This issue is currently most pressing within the context of the 20-week ultrasound.<sup>63,80</sup> As it is not realistic to discuss every possible outcome of the ultrasound with the pregnant woman in advance, the question arises whether a form of generic consent (see chapter 3) would suffice. The best approach to pre-test counselling is currently still being searched for. However, if the possibility exists to perform genome-wide testing of the foetus, starting with techniques such as array CGH, this challenge will only grow. The core question is whether the goal of prenatal screening (promoting

reproductive choice) is served or actually undermined by the trend towards broader prenatal testing.

Given these developments, it has been suggested that this will eventually lead to almost every pregnancy delivering a finding that forces the pregnant woman to decide on whether or not to abort, even if only because of a finding whose meaning is not yet clear. The paradox is that 'the quest for a health baby could cause parents to have no baby at all'.<sup>75</sup> There is certainly cause for concern about the degree to which increasingly broad prenatal tests, due to the sometimes difficult to interpret meaning of certain findings, may lead to unnecessary abortion decisions. Regardless, future parents will often still decide to have the child, even if they have been informed about (potential) weaknesses in its genome. Most pregnancies are desired and 'valuable', after all.

## **6.4 Testing of future children**

Precisely because knowledge about the foetal genome will often not lead to termination of the pregnancy, a new and until now unacknowledged problem presents itself: children born after genome-wide diagnostic testing or screening have already undergone far broader genetic testing than is considered justifiable for neonatal screening. Prenatal arrays can, for example, show that the future child has a genetic susceptibility for severe late onset disease, such as hereditary breast cancer. Further expansion based on whole genome sequencing may lead to children being born with a fully analysed genome. Everything allowed for by the current state of knowledge regarding the meaning of their genetic makeup for health prospects and traits partially governed by genetic factors (behaviour, cognition, personality) is in principle already known. This raises the same concerns associated with analysing the whole genome of newborns: the future child may not only be seriously harmed, but he or she will also be robbed of the choice to decide for him/herself, later in life, as an adult, about what he/she wants to know about his or her genome.

## 7 Genome-wide embryo screening

The introduction of increasingly broad testing may also be expected for screening of embryos created in the context of an IVF treatment. As broader tests become available, the question arises of which criteria should be used for selecting embryos that qualify for implantation in the uterus. Do doctors and future parents have the responsibility to choose the embryo with the best health prospects?

### 7.1 Pre-implantation genetic screening

In general, IVF produces more embryos than can be placed into the uterus responsibly in a single cycle. In order to limit the number of multiple births, only one or two embryos qualify for transfer per cycle. The best embryos are selected for this purpose; the rest – assuming they are of sufficient quality – can be frozen for a future attempt. When viewed in this context, embryo selection is as old as IVF treatment itself. Until recently, most centres selected primarily on morphological characteristics that appeared to be associated with a chance at a successful implantation in the uterus and therefore pregnancy and birth. However, because many IVF embryos have been found to have chromosomal abnormalities, and because (some of) these abnormalities correlate strongly with failed implantation and miscarriage, some centres started testing IVF embryos for relevant abnormalities (aneuploidy of certain chromosomes) over ten years ago, and only transferring those without abnormalities to the uterus.<sup>81</sup> The same procedures developed for examining embryos of couples with an elevated risk of transmitting severe hereditary conditions to their offspring are used: pre-implantation genetic diagnosis (PGD). However, unlike PGD (targeted testing with a specific indication), this is a routine test applied to all IVF embryos. In order to make the distinction clear, this is referred to as pre-implantation genetic screening (PGS), embryo screening in short.<sup>82</sup> The procedure is the same, however: in both cases, the embryo is sampled in a phase of ‘embryonic cleavage’; a cell is removed, examined, and if the outcomes are positive the embryo qualifies for transfer to the uterus.

In countries with commercial IVF practises, PGS has fast become a routine part of IVF treatment, particularly in the treatment of older pregnant women, in whom the percentage of embryos with chromosomal abnormalities is already highest. To date, more than ten trials have been performed showing PGS has no advantages whatsoever.<sup>81</sup> One possible explanation is the high percentage of mosaicism in embryos in the blastomere phase

(cleavage-stage embryos). Mosaicism means that abnormalities found in the sampled cell may not be representative of the embryo as a whole.<sup>83</sup> Consequently, PGS also leads to the rejection of embryos that do have a good chance of implantation. Introduction of the current approach therefore appears to have been premature. It has been proposed to investigate whether PGS does work if embryos are sampled at a slightly earlier or later stage (polar body and/or trophectoderm biopsy), but also to perform analyses using the broader testing options offered by array CGH. This is already being done in some clinics<sup>84</sup> and a multicentre trial has been set up by the European Society for Human Reproduction and Embryology (ESHRE) to determine the value of PGS based on polar-body biopsy and analysis with array CGH.<sup>81</sup>

Using microarray PGS, targeted testing of chromosome regions and genes important to implantation and the odds of pregnancy can be performed. This is the original and still the most important goal of PGS. As soon as such a broader test is used for PGS, however, this will also create the potential for looking at all manner of other hereditary characteristics. Despite practical limitations relating to the limited amount of time, and the fact that there is so little test material (a single cell), some expect it will – in principle – be possible to test embryos for:

- Genes and chromosomal abnormalities that are important for the odds of implantation and the chances of a successful pregnancy
- Other chromosomal abnormalities, such as Down syndromes
- Monogenetic abnormalities, including conditions that manifest early in life, but also late onset diseases such as Huntington's disease
- Genetic risk of multifactorial diseases, such as type 1 diabetes or asthma
- Genetic susceptibility associated with certain non-disease related traits.<sup>85</sup>

Initially, this will only involve genome-wide screening based on array CGH, but this is another area where implementation of genomic sequence analysis is conceivable, possibly with some form of filtering.<sup>86</sup> To allow this, current techniques for genetic testing of a single cell will first have to be improved significantly.

## **7.2 Selection of the 'best embryo'?**

To the extent that the PGS searchlight is set to a broader sweep, the goal shifts from selecting the embryo with the best chances of growing into a child, to the embryo most likely to grow into the healthiest possible child, to the embryo that will be the best possible child (with the definition of 'best' and who gets to decide on it remaining open for debate).

As there is always only a limited number of embryos available for selection, and because some of them are rejected already due to quality concerns relating to the odds of implantation and pregnancy, the room for selection based on other characteristics considered relevant remains limited. However, even if only two or three embryos remain after this initial selection

that qualify for transfer to the uterus, it can still be useful to consider which one scores best on other criteria believed to be important.

The broader the scope and the more stringent the desired selection, the fewer IVF embryos will qualify for transfer to the uterus. There is a very real possibility that among the available embryos with an acceptable chance of successful implantation, not one is present without any potential risks to the child's future health. This may lead to doctors and parents deciding to initiate a new IVF cycle, hoping this will lead to better embryos. Whether this can be justified will depend on the nature of the risks identified, and the proportionality of a new cycle (taking into account the associated material and immaterial costs) as a means for preventing said risks. And should this be limited to one new cycle, or can it be repeated as often as necessary until an embryo that is good enough is found? The immaterial costs, in addition to the burden and risks of a new stimulation cycle for the woman, include the larger number of embryos that will be necessary to fulfil the couple's desire for children.

It is clear this may lead to difficult choices and potentially to conflict between parents and doctors in daily practice.<sup>87</sup> If a choice has to be made between multiple embryos with a good chance of implantation, what should the criteria for making this choice be? Should health aspects be the only things considered, and if so, which ones? Can the choice remain meaningful if genome-wide testing is involved? Should the choice be left to the parents, or does the doctor have a separate responsibility in this area? What if parents want to select based on non-health related traits of the embryo, such as gender? Is this unacceptable in principle? Or only if it involves a form of selection that violates the right of the child to an open future?<sup>48</sup>

As is the case for genome-wide prenatal diagnostic testing and screening, the question arises whether this open future is not already threatened by analysing the entire genome of embryos that may be selected for transfer. How does this relate to the future individual's right to eventually decide for himself what he wants to know about his genetic makeup?



## 8 Familiar frameworks under pressure

The legal, ethical and social questions raised by the development of the thousand-dollar genome are not all new. What is new is that these developments appear to have consequences for the normative frameworks that guide policy on genetic diagnostic testing and genetic screening.

### 8.1 Familiar questions on a different scale

Seven years ago, in an early commentary on the search for the thousand-dollar genome and the normative implications thereof, American ethicist and jurist Robertson wrote that not only would it be another ten to fifteen years before technology was ready for fast and cheap analysis of the entire genome, but also that by that time, scientists 'will know a great deal more about what genes do and their connections with both single gene and multifactorial diseases'. Once the technology becomes available, it will lead to 'the same ethical, legal, and social issues that now arise with our more fragmentary knowledge of the genome and our more limited genotyping ability'.<sup>88</sup>

However, the reality of 2010 is that clinical introduction is already knocking at the door, while knowledge about the precise function of the genome remains extremely limited. The first steps are currently being taken. It is expected that in 2011, a few hundred patients in our country will undergo whole exome sequencing for the purposes of genetic diagnostic testing.\* It is therefore not true that society will have to deal with the implementation of the thousand-dollar genome only after the issue of noise has been resolved, the advantages (in terms of personalised medicine) are clear and the only thing that needs to be clarified is how to prevent certain undesirable consequences. This ignores not only the medical reasons currently leading to genome-wide diagnostics, but also the driving forces and motives behind the movement towards increasingly broad screening of newborns, young adults, fetuses and embryos.

And what about Robertson's comment that the implementation of the thousand-dollar genome in daily practice will not raise any new normative (ethical, legal) questions. Is it true? In part, it is. Problems surrounding unsought and potentially unwanted findings, the feasibility of informed consent, the right to not know, informing relatives, recontacting, whether or not to

\* Professor RA Wevers, University Medical Centre Nijmegen, personal message

test children, etc. already exist now. Viewed in this context, it is primarily a question of scale: implementation of genome-wide testing makes the challenges bigger and more complex. This means old answers may not suffice, or new solutions may need to be sought. For example, can the generic consent model be elaborated to allow for meaningful consent for genome-wide diagnostic testing? Or is the idea that well-considered consent will remain possible for tests that can reveal information about the entire genome an illusion? What does this mean for the acceptability of such tests? Is giving up on anything more than marginal informed consent the price we have to pay in order to benefit individually and as a society from the advantages of personalised medicine?

A second marginal note to Robertson's comment is that what is seen as a relevant ethical or legal question or consideration is partly dependent on the normative frameworks that form the perspective we normally use to thematise certain issues. The previously outlined developments shake up these frameworks and put them under pressure. This means that, unlike what Robertson suggests, how the implications of the developments described in this report should be dealt with is far from self-evident.

## **8.2 Diagnostic testing with additional findings, or screening with a diagnostic indication?**

A key distinction that will be put under pressure by the introduction of the thousand-dollar genome is that between diagnostic testing and screening. The former is conducted within the context of individual patient care, in response to a complaint, based on previous findings or family history; the latter encompasses the unrequested offering of medical testing to an as yet unaffected population. If genome-wide analysis is used because it is the only way to determine the genetic background of a poorly understood health problem in an individual patient, the motive remains *diagnosis*. However, given the fact at most a tiny amount of all health information this delivers will have anything to do with the specific problem being investigated, the procedure also closely resembles a form of (undirected) *screening*. Practically all findings relevant to the subject's health prospects will, after all, not have been searched for with a reason.

This is important when considering the question of what perspective should be used to examine the justifiability of (offering) such testing. Is this diagnostic testing with inevitable additional findings? In this case, the key question is whether the approach selected is the best way to obtain information about the health problem in question, and a pragmatic solution will need to be found for how to deal with all additional information yielded by the study. The question is whether these outcomes can be termed 'additional findings' if they encompass almost *all* of the test outcomes. Would it not be better to refer to it as genome-wide screening with a diagnostic indication? That this formulation, given the previously given definitions of diagnostic testing and screening, comes close to being a *contradictio in terminis*, is not merely an issue of semantics. It shows that the familiar borders between these different forms of



medical testing are under pressure due to the developments described, with potential implications for normative assessment thereof. If these tests are (also) a form of screening, should they not be assessed from within the normative framework developed for screening (see 8.3)? At the very least, should not the question be asked whether the importance of elucidating the individual's initial problem weighs more heavily than the potential disadvantages of genome-wide testing? Is this a consideration that can be left to the patient? Even if this is the case, the distinction between a 'diagnosis perspective' and a 'screening perspective' may lie in the emphasis with which the consideration and the potential implications of various outcomes are shared with the patient. The issue becomes even more complex with genome-wide diagnostic testing of (young) children. If this is also a form of screening, the previously mentioned objections to genome-wide screening of newborns and children come into play. Or does the fact medical diagnostic need was the indication for the genome-wide testing change things in these particular cases?

That genome-wide diagnostic testing is difficult to differentiate from screening and raises a number of difficult questions traditionally associated with the normative framework developed for screening at the very least means that the move towards genome-wide diagnostic testing demands even more explicit justification in terms of medical necessity, proportionality and subsidiarity. The latter means genome-wide diagnostic testing should only be considered if it is clear that testing with a narrower scope (using filters) will yield insufficient results.

### **8.3 Genome-wide screening in the context of the existing normative framework**

Screening is defined as: 'the provision of medical testing to persons who in principle have no health complaints, focused on early identification (or ruling out) of already present disease, hereditary predisposition for disease or risk factors that increase the odds of disease'.<sup>16</sup> Conditions for responsible screening were first formulated in the 1960's by Wilson and Jungner for the World Health Organisation, and later developed and modified further by various authors and organisations (including the Health Council<sup>35</sup>), primarily taking into account developments in the fields of genetic and reproductive screening. The Health Council advisory report 'Screening: between hope and hype' summarises the key principles as follows:

- screening must be focused on a significant health problem;
- benefit: it must be clearly established that early detection of the illness(es) or condition(s) in question (or: detection of medical conditions such as carrier status or risk factors) can lead to a significant reduction in the burden of disease in the target group in question, or to other outcomes useful to the participants in the context of the medical problems to which the screening relates; these advantages must clearly outweigh the disadvantages that screening can always have (for themselves or for others);
- reliable and valid instrument: the screening method must have a solid scientific basis and the quality of the various parts of the screening process must be guaranteed;
- respect for autonomy: participation in screening and follow-up tests must be based on an informed and free choice; supply and performance must respect patients' rights (in the case of services offered outside the healthcare system: consumers' rights);
- appropriate use of resources: the use of available healthcare resources in connection with and because of the programme must be clearly shown to be acceptable in terms of cost-effectiveness and justice.

Source: Health Council of the Netherlands. Screening: between hope and hype. The Hague: Health Council of the Netherlands, 2008. Publ. Nr 2008/05E.

Where does genome-wide screening fit into this framework? Genome-wide screening is defined as: analysing the entire genome (ultimately based on a full sequence analysis). In order not to make the discussion more complex than necessary, we are basing the following on a scenario where such screening would be offered routinely to (young) adults. Specific questions relating to neonatal screening and screening of foetuses or embryos are addressed later in this chapter.

The first condition, that screening must target a significant health problem, can strictly speaking not be met as this form of screening does not target a specific condition (or conditions). This also strains the other conditions outlined in the normative framework. To begin with, the question of utility (the second condition in the framework in question). Some of the findings will be information that can lead to immediate health gain or gains later in life, or allow avenues for action viewed as useful by the part involved, for example lifestyle changes or reproductive choices. However, the information will inevitably also include findings that are a burden to the party involved, even potentially harmful (in a social context) information about a predisposition for or chances of developing serious, untreatable conditions, information about the genetic basis for non-health related traits, as well as findings for which the precise (health) implications are unclear or unknown. Given these potential outcomes, how to determine whether the advantages outweigh the disadvantages for the individuals to be tested?

When weighing the disadvantages, the potential consequences of imperfect testing methods must be considered, including unnecessary worry and other negative consequences (unnecessary follow-up testing, unnecessary preventive measures, unnecessary costs) of false-positive outcomes, overdiagnosis and false reassurance caused by false-negative outcomes. This is why a reliable, validated instrument is necessary (the third condition from the normative framework). How should this condition be assessed with regard to sequencing and analysing the entire genome? Firstly, it is important to note sequencing has its limitations, certainly using current techniques. This means potentially relevant information (such as translocations and other structural variation) may not be found.<sup>89</sup> Secondly, because the analysis examines a broad array of not always fully well-understood, more or less rare health effects, the question of testing method validity and predictive value for outcomes does not have an easy answer. Some findings are directly predictive, while the predictive value of many others, particularly with regard to common conditions, will be slight at best.<sup>36</sup> Thirdly, as interpretation of results is reliant on still limited, but thanks to new research growing knowledge about various forms of genetic variation, some conclusions, for example regarding personal health profiles and health recommendations, will have to be adjusted as new insights are gained.<sup>89</sup> This speaks directly to another quality aspect: post-test counselling and care for people who have had their genome analysed is likely the greatest challenge related to this development.<sup>39</sup>

The fourth condition is that participation in screening must be based on an informed, well-considered choice (informed consent). Even if taking the time for routine, extensive multidisciplinary counselling is a realistic option<sup>89</sup>, obtaining anything beyond a form of generic consent appears unfeasible. The information that would need to be provided would have to generally outline (1) types of findings, (2) types of consequences (treatment options, reproductive choices, preventive options, psychosocial and social risks, consequences for relatives) and (3) limitations, including the fact new insights may lead to adjusting the conclusions. The question is whether this is enough to allow a considered choice to be made about the offer to analyse the personal genome. The 'right to not know' in particular will be difficult to shape in this context.

The fifth and final condition from the screening framework relates to the effectiveness of screening in relation to the burden it places on collective means. There needs to be a positive balance between yield – in terms of health gain or other useful treatment options – and net costs. When looking at costs, it is clear one must look beyond the costs of sequencing alone (the thousand-dollar genome), but also include the costs of analysis, pre-test and post-test counselling, the costs of follow-up testing and intervention, as well as any savings, for example due to timely prevention (lifestyle adjustment) or more targeted use of medication.<sup>16</sup> As it is still practically impossible to comment on most of these factors, this demand can currently not be met.<sup>38,90</sup>

## 8.4 Undirected screening, clinical check or a right to information?

If analysing the personal genome should be viewed as a form of screening, it becomes clear that the undirected nature of such a test can strain the principles of the previously discussed framework. However, not all participants in the debate are convinced this development should be viewed from this perspective. There are two competing perspectives. First, there is the ideal of personalised medicine. The belief that explicit justification is required for providing unasked for predictive medical testing to people who do not have any complaints or other reasons to (want to) undergo such testing, will no longer be obvious for those who believe that it is in everyone's best interest to be aware of their health risks. And that it is the responsibility of the medical field to find out about these risks as a basis for an integral form of health management. Viewed in this light, it is easy to understand why publications about analysing the genome of a 40 year-old man (see 4.2) refers to the clinical assessment of a patient<sup>36,89,90,90</sup>, despite the fact he has no health complaints and there was no concrete indication for medical testing. Reasoning from the ideal of tailored medicine, everyone is a patient from cradle to grave. The distinction between screening and patient care then loses all meaning.

This (medicalised) way of looking at things does mean that an interest is created (the patient's interest in good care) which immediately guides the debate about the usefulness of analysing the entire genome in a particular direction. This is reflected by what is said about the usefulness of the pharmacogenetic information obtained about the 'patient': data on genetic factors that lead to a better or worse response to certain medicines.<sup>90</sup> Note: the man in question does not use any medication. Furthermore, such information could be searched for in a targeted fashion as soon as certain medication appears necessary. If this were considered screening, this consideration would at the very least question the supposed usefulness of the procedure. This conclusion is not drawn here. On the contrary: the emphasis is placed on the fact the genome of this 'patient', in addition to 63 known ones, also yielded 6 new genetic variants important for the response to medication that would not have been found using a targeted pharmacogenetic test (using current levels of knowledge).<sup>90</sup> Of course, this is an important discovery that can contribute to improving care for future patients. But the focus here should be on the supposed benefits for the individual. Only by labelling him as a patient can the implication that these discoveries have yielded clinically relevant information that contributes significantly to the usefulness of analysing the entire genome be maintained.

There is also another way of looking at the issue, which is propagated among others by commercial providers of genetic tests and dovetails neatly with the previous viewpoint. The key issue is that people who want to know should be able to gain knowledge about themselves, and that there should not be unnecessary barriers in their way. From this perspective, the normative framework – particularly the requirement that the advantages of undergoing medical testing must clearly outweigh the always present disadvantages – is viewed as a problematic form of paternalism. Why should the individual in question, after being

informed fully, not be able to make this choice himself? Does being able to obtain personal (genetic) information not relate to every individual's right to a private life, as recognised by the Dutch Constitution and the European Convention for the Protection of Human Rights and Fundamental Freedoms?

The Population Screening Act (WBO) has previously been criticised in this context, as it states that a license is required for certain forms of (potentially high-risk) screening, based on the requirements outlined in the normative framework discussed above (8.3). The previous debate was engendered by the total body scan: undirected imaging screening using a CT scan or MRI. As no license was issued, Dutch citizens who believe such a (regular) scan has preventive value must travel abroad to obtain it. Reasoning from within the normative framework for screening and the protection goal of the WBO, the Health Council took the position that as long as there is no scientific evidence for clinical usefulness, the inevitably present disadvantages (false-positives, unnecessary worry, false reassurance, overdiagnosis, iatrogenic harm) plead against issuing such a license.<sup>16,91</sup> Others view the protection strived for in the WBO as an unjustified limitation of the individual's right to know.<sup>92,93</sup> It appears inevitable that this debate will be revitalised as a market for analysing personal genomes develops.

As long as personalised medicine remains a largely unfulfilled ideal, and as long as the cost-effectiveness of analysing whole genomes remains unclear, offering such testing using public means is not an option. For this reason, the British Human Genetics Commission views analysing personal genomes (in adults) as solely lying in the domain of commercial parties, building on the already available commercial offerings of SNP-based genetic susceptibility profiling.<sup>38</sup> The committee follows the reasoning that this essentially relates to not limiting the rights of individuals to obtain information about themselves without good reason. In the Netherlands, the WBO would require licensing for such commercial offerings as well, which would need to be assessed within the normative framework discussed above and would therefore not be issued easily.<sup>16</sup> The resulting *de facto* ban will be easy to circumvent by commercial parties operating outside the Netherlands using home collecting tests\*.

## 8.5 Reproductive and non-reproductive screening: no longer worlds apart

Prenatal screening, embryo screening and preconceptional screening of (young) adults for carrier status of recessive conditions are forms of reproductive screening. Reproductive screening has the goal of allowing involved parties to make useful choices with regard to reproductive risks. This is a key difference compared to non-reproductive screening, which (usually) has the goal of obtaining health gains for the individuals being tested.

These distinct categories of screening are associated with diverging normative frameworks. Non-reproductive screening focused primarily on health gains (such as screening in youth

\* For which self-collected test samples such as cheek swabs or blood must be sent to a laboratory.

health care, but also existing population screening programmes for breast and cervical cancers) is rooted in public health care: collective facilities focused on reducing disease burden. The usefulness for society and for the individual generally line up for this type of screening. Striving for a high, positive response to the screening programme is not seen as problematic, as long as participation is voluntary and based on informed consent. In the Netherlands, this requirement also applies to neonatal screening. In some other countries, it is assumed parental consent is not required when it comes to screening for severe conditions of early childhood that can easily be treated or prevented if detected early enough. After all, parents can be expected not to withhold such screening from their child.

Reproductive screening, on the other hand, traditionally has strong roots in the context of individual genetic counselling and reproductive counselling. In normative terms, this is a different world, with a strong emphasis on the personal character of reproductive decisions (particularly: the decision on whether or not to carry the pregnancy to term) and on the ideal of professional non-directiveness. The individual's personal, well-informed choice is not merely an important precondition; enabling this choice is the primary goal of the screening itself.<sup>41,63</sup> At the same time, monitoring this is considered an important challenge, because the interests of individuals and society are less self-evidently in line than is the case for non-reproductive screening focused on health gains. The potential that social goals (particularly cost reduction by preventing the birth of handicapped children) could undermine the goal of reproductive screening (enabling autonomous reproductive choices) is generally seen as a significant threat to the moral tenability of screening offerings.<sup>28,63,94</sup> Finally, an important distinction is that while non-reproductive screening for conditions for which there is no treatment or prevention is considered problematic, reproductive screening is often specifically focused on such conditions. Non-reproductive screening for such conditions is problematic because it is likely to cause test subjects more harm than good; this could also affect the anticipatory autonomy rights of a child.

### **Strain between normative frameworks in the screening of newborns**

To date the briefly mentioned normative frameworks for reproductive and non-reproductive screening (essentially sub-frameworks of the general normative framework for responsible screening described under 8.3) existed side by side without many problems, as the worlds generally did not overlap. This appears to be changing. The first overlap is found in the previously outlined debate on expanding neonatal screening to include conditions of early childhood for which there is no treatment or prevention (See 5.3). Given the most important motive for expansion is informing parents of their repetition risk, traditional non-reproductive (focused on the health of the child) screening gains a reproductive goal. This creates overlap between the above-mentioned normative frameworks. While the traditional goal of neonatal screening is easy to reconcile with a directive approach to parents who do not wish to have their child screened, expanding screening offerings at least in part relates to tests that may not be forced onto parents. Various commentators have pointed out the risk of various messages crossing each other.<sup>95-97</sup> Parents might believe that screening for untreatable conditions is

something they should not be allowed to abstain from. Conversely, they might lose sight of the fact at least part of the offerings are not without obligations.

### **Strain between normative frameworks in analysing personal genomes**

A second development that may lead to overlap between the normative frameworks described is the hypothetical scenario of analysing personal genomes as routine care upon reaching adulthood.<sup>37</sup> A single test procedure could then provide information about both avoidable reproductive risks and information important for the individual's personal health prospects. As long as this is a service focused on individuals who want to obtain important information about themselves (see 8.4), tension between underlying normative frameworks may not be an issue. Simply informing people about their health risks would seem to dovetail neatly with the goal of reproductive screening: providing practical courses of action. The question is, however, if what each individual does with this information will be seen as a choice to be respected that society has no say in. This does not appear likely. An inevitable implication of the ideal of personalised medicine is that – even more so than is currently the case – the emphasis will lie on personal responsibility for good health. Advocates for this ideal are clear: 'Personal choices have a profound impact on your health, and they are your responsibility'.<sup>39</sup>

A more realistic elaboration of the scenario above is that analysing personal genomes will (in part) become a public health instrument. Not only will people be expected to want to obtain relevant health information about themselves, but also to use said knowledge to improve their health prospects wherever possible. If this becomes the dominant perspective, the question arises whether there is still room to address information affecting reproductive choices, such as carrier status for recessive conditions, in a completely separate way. Will it still be self-evident that people must be allowed to make a choice 'that *they themselves* believe to be good and prudent' when it comes to reproductive decisions?<sup>42</sup>

### **Strain between normative frameworks in genome-wide prenatal diagnostic testing and screening**

A third development where overlap between existing normative frameworks is developing is the potential introduction of genome-wide tests within the context of prenatal diagnostic testing and screening. From the perspective of the traditional normative framework, this immediately raises difficult questions. Is a true informed choice a feasible option for the pregnant woman and her partner? Will genome-wide tests not lead to abortion decisions based on outcomes for which the exact health implications for the future child are still entirely unclear? Is this not the polar opposite of providing practical courses of action? An almost equally important question is not even raised in this context: is it acceptable to analyse the whole genome of future children, including all available information on health problems that can be expected later in life, before birth? In addition to enabling future parents to make useful reproductive choices, should not the interests of the future child be considered?

That this child is yet to be born is irrelevant. After all, the interests of the future individual can already be harmed during (or even before) the pregnancy.<sup>98</sup> In other contexts, increasing attention is being given to protecting these interests. For example where potential health harm to the future child due to an unhealthy lifestyle of the pregnant woman is concerned.<sup>99</sup> It would therefore be inconsistent to ignore this violation of the autonomy rights of future individuals that will inevitably follow the introduction of genome-wide prenatal testing. But in order to be aware of this problem, the perspective must be broadened. An adequate ethical analysis requires the justification for genome-wide prenatal diagnostic testing or screening also to be considered from the perspective of the normative framework applicable to the testing of children.

The problem in question is familiar from the debate surrounding targeted prenatal testing for the gene for Huntington's disease.<sup>28,100</sup> If the test has an unfavourable (positive) outcome, most parents will choose to abort the pregnancy. If they do not, however, they will have a child who – before birth – has already undergone a presymptomatic test for an extremely severe and untreatable late onset disease. Given the previously mentioned consensus that it should not be allowed to test children for such conditions, the question arises whether care providers can offer prenatal diagnostic testing in a responsible manner if a potential outcome is the birth of a child who is tested for those conditions. The same problem arises for prenatal diagnostic testing for a number of other autosomal dominant conditions, including the hereditary (often early onset) form of Alzheimer's disease.<sup>101</sup> The solution chosen to address these complex situations, contrary to standard practice for prenatal diagnostic testing, is to only allow future parents access to the test on the condition they plan to abort the pregnancy in the event of an unfavourable result.<sup>102</sup> Of course, conditional access to prenatal diagnostic testing does not mean future parents can be forced to terminate the pregnancy in the event of an unfavourable result.

Although the problem (obtaining information not limited to diseases only occurring early in life or requiring early treatment or prevention) is not entirely new, there are two important differences compared to past debate. First, genome-wide prenatal screening (and diagnostic testing) engenders a 'systemic' problem that will apply in all cases where the decision is made not to terminate the pregnancy. Second, conditional access is not a workable solution in this case. After all, once the entire foetal genome has been analysed, carrying the pregnancy to term will inevitably entail a violation of anticipatory autonomy rights. There appears to only be one solution to limiting this rights violation wherever possible when implementing prenatal tests based on whole genome sequencing: using filters during analysis. The entire genome is then sequenced prior to birth, but not fully analysed. Ideally, filters should be implemented so that they only yield information about conditions manifesting early in life or requiring early initiation of treatment or prevention.

A question remains whether the distinction between genome-wide prenatal diagnostic testing (for example after an abnormal 20-weeks ultrasound) and genome-wide prenatal screening



(offered without indication) affects the justifiability of violating anticipatory autonomy rights. This appears to relate to the reason for choosing genome-wide diagnostic testing. Is the goal solely to inform the pregnant woman (and her partner) as fully as possible in order to allow a well-considered decision about whether or not to carry the pregnancy to term? Or are the future child's health interests also at stake? The latter case creates different considerations than if genome-wide diagnostic testing does not serve the child's interests at all.

### **Strain between normative frameworks in genome-wide embryo screening**

While prenatal tests can require one to choose whether or not to allow a child to be born, embryo screening involves deciding to let *this* specific embryo rather than *that* one to grow into a child. This is a different type of choice. While aborting the pregnancy (within the confines of the Abortion Act) is rightfully seen as a highly personal decision that in principle neither the care provider nor society have any say in, this is less clear for the choice presented here.<sup>103</sup> Assume there are multiple embryos with equally good chances of successful implantation. Is the choice of which embryo to place into the womb morally neutral? This would be the case if we did not know anything else about the embryos, but this is precisely what may change with the introduction of genome-wide tests. Assume the entire embryonic genome has been analysed. Could the parents and involved care providers then not be expected to choose the embryo with the best health prospects or the highest quality of life?<sup>104</sup> Even if this is not in the interests of the child itself (the child by definition cannot be born with a better genetic makeup than it has), the question arises whether there are social interests to consider. This also has consequences for the question of how widely to cast the searchlight of the test used for embryo screening. A narrow beam would mean pre-emptively missing out on the possibility to select the embryo with the best chance of a healthy and happy life. What about the doctor's role? In principle, prenatal diagnostic testing and screening demands a non-directive stance from involved care providers. In this scenario, however, the doctor is jointly responsible for the creation of the future child.<sup>105</sup> Does this make a directive approach less problematic? Can the doctor present wide scope (possibly genome-wide) embryo screening as self-evident? Would it be acceptable for society to become involved in the process? What if insurance companies demand optimum use is made of the possibility to select an embryo with the best possible risk profile as a condition for covering the costs of IVF?<sup>103</sup>

It is important to note that the choice between embryos cannot be avoided. No pregnant woman, no future parents are obligated to undergo prenatal screening. But having a child through IVF implies embryo screening. After all, one (sometimes two) embryos will have to be selected regardless. To date, this is based on morphological quality criteria not extending beyond the odds of implantation and pregnancy. However, as soon as tests become available that can also be used to select for a broad range of genetic factors relevant to the future child's health prospects, the question of what a good choice is, and therefore what a good embryo is cannot be avoided.

This gives rise to complex problems that require deeper consideration. First and foremost, it appears the classic normative framework for reproductive screening will be strained in this specific context. The ideal of allowing autonomous reproductive choices appears less suitable for guiding this new practice than the idea of making future parents and care providers jointly responsible for making a good choice. What criteria should apply to defining this 'good choice' remains the core issue. That society will primarily want this question answered from a public health perspective is a realistic assumption.

Secondly: the problem of testing future children and the potential harm to their anticipatory autonomy rights appears to be an even greater challenge in this context than with regard to genome-wide prenatal diagnostic testing and screening. The use of filters could once again be proposed as a solution to only obtain information about conditions manifesting early in life or requiring early initiation of treatment or prevention. But does not the idea of having to select the best possible embryo stand diametrically opposed to filtering out information that may be relevant to health prospects, including long-term ones, of the future child?

Given the outlined developments, the fact pre-implantation genetic screening (PGS) is not covered by the Population Screening Act (WBO) is an significant regulatory gap. This is because it is not a test performed on people, and is therefore not population screening in the context of the law.<sup>82</sup> This is not necessarily a major issue as long as screening is focused solely on chromosomal abnormalities that affect the odds of implantation and successful pregnancy, but the situation changes for wider, certainly for genome-wide embryo screening. Although the tests are not performed on people, the fact they will lead to the birth of children with a fully analysed genome appears to be a good reason to bring this form of screening under the purview of the law.<sup>103</sup>

## **8.6 Blurring borders between care and research**

As described in chapter 5, the plea for further expansion of neonatal screening is in part coming from researchers who expect large-scale screening of newborns for all kinds of rare conditions could make a significant contribution to elucidating the causes of those diseases and the development of treatments. The importance of such research (for society, for children who could potentially benefit from the results of such research) is obvious. But is it a valid reason for expanding screening of newborns? According to the advocates for this approach, the answer is clear. They see the classical assumption, that screening of newborns must benefit the individual child as a barrier to scientific progress:

There is hope of developing and evaluating effective therapies only with early presymptomatic identification of the disorder and the availability of sufficient numbers of presymptomatic patients with rare disorders that a registry can provide. The old dogma cannot be allowed to stand in the way of developing effective treatments for these rare genetic disorders.<sup>52</sup>

As this quote demonstrates, obtaining a research population that is as large as possible appears to be the primary goal of the plea for expansion. After screening, the next step is to include children with specific genotypes in a large-scale research registry (genetic database, bio bank) that can be used to study genotype-phenotype correlations.

The conditions under which children (with proxy consent from their parents) can be included in bio bank research is still being debated.<sup>54,106,107</sup> The main issue here is that it becomes impossible to determine where screening (healthcare) stops and scientific research begins.<sup>51,108</sup> The question of whether the trend towards increasingly broad tests is in part driven by the need to obtain data for scientific research also applies to other forms of diagnostic testing and screening. As long as this is a supplemental goal that does not itself determine the scope of the test, this does not have to be a problem. The discussion above does demonstrate that the goals of healthcare and science can easily cross paths. The same issue exists for commercially offered direct to consumer tests: consumers often are unaware that their data is being used for scientific research.<sup>109</sup>

## 8.7 Predictive information about behaviour

Genome-wide diagnostic testing and screening will doubtless also yield results in the field of behavioural genomics. This may include behaviour that falls under or relates to the medical domain, such as addiction, as well as behaviour where this is not or at least not obviously the case, such as anti-social behaviour. The debate about the potential advantages and disadvantages of predictive tests for genetic predisposition to addictions and anti-social behaviour is still in its infancy.<sup>50</sup> Some feel the debate is untimely or premature, primarily because the predictive value of currently identified genetic risk factors is low.<sup>39</sup> It must be considered that future combined tests, in which predictive genetic testing is linked to psychological tests, for example, could lead to risk profiles with a (very) significant predictive value. Proponents emphasize that early identification would allow primary prevention, a win-win situation in which all parties benefit – the person with a predisposition for the behaviour to be avoided as well as his or her environment. It is important to note a balanced assessment must also include the potential disadvantages of early detection. What about false-positive test results? Can identifying high-risk individuals not cause stigmatisation? What about the risk of a self-fulfilling prophecy?

Regardless, the potential future introduction of predictive genetic testing for (problem) behaviour requires embedding in scientific research in order to systematically examine and weigh the potential advantages and disadvantages.<sup>110</sup> Given the interests involved and the potential risks for individuals, great care is required. Particular attention is needed for the interests and (future) autonomy of the children who could potentially be involved in such research.

The required care would be ignored completely if genome-wide diagnostic testing and screening were to deliver genetic information about the hereditary susceptibility to (problem)

behaviour as a by-product without multidisciplinary scientific research to determine its value, relevance and impact.

## 9 Conclusions

Even if the question of whether all expectations raised by the ideal of personalised medicine will be realised remains open, the developments described in this monitoring report appear to have potentially far-reaching consequences, not only for future developments in healthcare, but also for individuals and society as a whole.

Genome-wide diagnostic testing can deliver useful information about poorly understood diseases and improve the prognosis of and treatment options for patients. But it will inevitably also yield all kinds of unsought information that is potentially burdening or even harmful for the patient (and his or her blood relatives). This raises the question of what conditions must be met for responsible use of such testing. It is currently insufficiently clear whether meaningful informed consent is possible in this context, how the 'right to not know' can be given form, and how the obtained information can be handled in a responsible manner. The questions become all the more pressing where genome-wide diagnostic testing of children is concerned.

Genome-wide screening, the analysing of the entire genome without medical indication, appears to have more disadvantages than potential advantages for the parties involved at this time. Offering such screening as part of standard healthcare cannot be justified at this time. However, as whole genome sequencing costs drop, commercial offerings based on genome-wide tests are to be expected. The question is how this affects the role of the government. Is its primary task in this context to protect citizens from unsuitable screening, or should they be left free to determine what information they want to obtain about themselves?

Where genome-wide screening of adults already leads to difficult questions, the issue is magnified when it comes to children, for example in the scenario of genome-wide heel prick screening. The question becomes not only whether the people making the decision can oversee the Pandora's box they are opening, but also whether they have the right to make that decision for their children. An important distinction between screening and genome-wide tests in the context of diagnostic testing is that there is no indication for such a broad test for the former. The potential benefit of analysing genetic characteristics that may be relevant for all kinds of personalised medicine as early in life as possible is itself not sufficient justification. Even if increasing understanding will make this a stronger argument in the future than it is now, the question remains whether the intended advantages outweigh the potential harm caused by burdening information or information that can otherwise negatively affect the child

in question. Third party interests, including the desire of parents to know as much as possible about the genetic makeup of their child, or those of scientific research, may not play a decisive role when coming to a decision.

Analysing the entire genome of future children may be the unintended consequence of genome-wide diagnostic testing and screening offered during pregnancy in the context of making an informed abortion decision. The question is what the potential violation of the child's 'anticipatory autonomy rights' should entail for the acceptability of genome-wide prenatal testing. Does the distinction between diagnostic testing and screening matter? The autonomy of the future child is also affected by the potential widening of the scope of embryo screening in the context of IVF. This involves the question of which embryos qualify for implantation into the uterus. Do doctors (and future parents) not have the responsibility to choose the embryo with the best health prospects? Conversely: are they allowed to analyse the entire genome of embryos that may grow into a child?

The questions raised by the discussion of the potential applications of the thousand-dollar genome are not all new, although the scale of the challenges is. More important is what is happening with the familiar normative frameworks normally used to thematise and answer such questions. They are under pressure, starting to overlap or run into each other. Relative to the developments discussed in this monitoring report, they appear to be losing at least part of their organising capacity and guiding character. Although some of the developments discussed are problematic when viewed from within these frameworks, there is also room to ask whether review or recalibration of these frameworks is necessary, should we wish to continue providing guidance for the application of scientific knowledge in healthcare.

Further reflection on the developments outlined and the normative implications thereof for all parties involved, including clinicians, scientists, jurists, ethicists, patient organisations and policy makers is of great importance. To begin with, there is a need for guideline development by the professions involved in the application of genome-wide diagnostics in adults, children and foetuses. The most current question is how to responsibly deal with unsought for outcomes of such diagnostic testing. Given the complexity of the matter, in both normative and scientific terms, there is also a need for more comprehensive reflection and debate.

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# Annex 1

## Standing committee on Medical Ethics and Health Law

- Prof. L.J. Gunning-Schepers, President of the Health Council of the Netherlands, The Hague, *chair*
- Prof. J.K.M. Gevers, Professor emeritus of health law, Academic Medical Centre, University of Amsterdam, *vice chair*
- A.C. de Die, lawyer, Pels Rijcken & Droogleever Fortuijn advocaten en notarissen N.V., The Hague
- Prof. J.C.J. Dute, Professor of health law, University of Amsterdam
- P.G. Engels, Ministry of Health, Welfare and Sports, *observer*
- Prof. R.P.T.M. Grol, Professor of quality promotion and control in general practice, St Radboud University Medical Centre, Nijmegen
- Prof. G.R.J. de Groot, Professor of social health care insurance law, VU University, Amsterdam
- Prof. G.A. den Hartogh, Professor of ethics, University of Amsterdam
- Prof. A.C. Hendriks, Professor of health law, Leiden University/health lawyer, Equal Treatment Commission, Utrecht
- Prof. H. Jochemsen, Professor of Christian reformed philosophy, Wageningen University, Wageningen
- Dr. W.L.M. Kramer, paediatric surgeon/paediatric traumatologist, Wilhelmina Children's Hospital, University Medical Centre, Utrecht
- Prof. F.E. van Leeuwen, Professor of epidemiology, Netherlands Cancer Institute, Amsterdam
- Prof. J. Legemaate, Professor of health law, Academic Medical Centre, University of Amsterdam
- Dr. G.C.M.L. Page-Christiaens, gynaecologist, University Medical Centre Utrecht
- Prof. MA Verkerk, Professor of medical ethics, University Medical Centre Groningen
- Prof. G.M.W.R. de Wert, Professor of biomedical ethics, Maastricht University
- A. Wijbenga, executive director of the Health Council of the Netherlands, The Hague, *advisor*
- Prof. D.L. Willems, Professor of medical ethics, Academic Medical Centre, University of Amsterdam

- Dr. C.J. van de Klippe, Health Council of the Netherlands, The Hague, *secretary*
- Dr H.W.J.M. Wijsbek, Health Council of the Netherlands, The Hague, *secretary*

# Annex 2

## CEG publications

### Monitoring reports

MONITORING REPORTS ETHICS AND HEALTH

#### 2009:

*Health Council of the Netherlands*

- He who pays the piper calls the tune? On funding and the development of medical knowledge
- Care for the unborn child. Ethical and legal aspects of fetal therapy

*Council for Public Health and Health Care*

- So far away and yet so near? Ethical considerations in care at a distance

#### 2008:

*Council for Public Health and Health Care*

- Farewell to non-commitment. Decision systems for organ donation from an ethical viewpoint

#### 2007:

*Health Council of the Netherlands*

- Should blood donors be tested for Variant Creutzfeldt-Jakob disease?

*Council for Public Health and Health Care*

- Appropriate evidence. Ethical questions concerning the use of *Evidence* in health care policy
- Financial incentives for organ donation

#### 2005:

*Health Council of the Netherlands*

- Embryonic stem cells without moral pain?
- Ethical aspects of cost-utility analysis
- Now with extra bacteria! Food products with health claims

*Health Council of the Netherlands/Council for Public Health and Health Care*

- Tracking down threats to health: screening in GP practice (RVZ)

*Council for Public Health and Health Care*

- Health care professional and police informant?
- Ethics in health-care institutions and in the education of care professionals

**2004:**

*Health Council of the Netherlands*

- Terminal sedation
- Advanced homecare technology: moral questions concerning an ethical ideal

*Council for Public Health and Health Care*

- Intermezzo
- Advanced homecare technology: moral questions concerning a new healthcare practice

These publications can be downloaded from [www.ceg.nl](http://www.ceg.nl), [www.rvz.net](http://www.rvz.net) or [www.gr.nl](http://www.gr.nl).