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# The iterative informed consent model for the feedback of incidental findings in human health research using WGS procedures

## *El modelo iterativo de consentimiento informado para hallazgos incidentales en la investigación clínica con secuenciación genómica completa*

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**Abstract**

Facing the upcoming application possibilities of genomic sequencing in human health research, to determine the appropriate ethical scope of genetic counselling for research participants becomes a most important challenge. In this thesis, an informed consent model for the disclosure of incidental findings in research using whole genome sequencing or whole exome sequencing will be presented.

The design of an informed consent model is always based on a general informed consent theory. Thus, informed consent models can be defined as application of an ideal informed consent theory, containing general ethical principles, to a particular context.

The aim of the thesis is to design and defend an inform model that determines the appropriate ethical scope of genetic counselling process for the disclosure of incidental findings –which I call the iterative feedback model due to the continuous informed consent process for the disclosure of incidental findings between counsellor and individual research participant. For this purpose, informed consent theories will be analysed and adapted to the case of human health research using whole genome/exome sequencing. Furthermore, relevant values of research ethics and characteristics of genomic data will be taken into consideration. The iterative model of informed consent is based on the traditional and on the dynamic consent models to ensure understanding and autonomous choice by research subjects.

**Resumen**

Frente a las posibilidades inmediatas de aplicación de la secuenciación genómica en la investigación en salud humana, determinar el alcance ético apropiado del asesoramiento genético ("counselling") de participantes se convierte en una cuestión de la mayor importancia. En esta tesis, se presentará un modelo de consentimiento informado para la divulgación de los hallazgos incidentales en la investigación que utiliza procedimientos de secuenciación del genoma completo o secuenciación de exoma completo.

El diseño de un modelo de consentimiento informado se basa en la teoría general del proceso de consentimiento informado. Por lo tanto, los modelos de consentimiento informado pueden definirse como una aplicación de la teoría de consentimiento informado ideal, que incorpora principios éticos generales, en un contexto particular.

El objetivo de la tesis es diseñar y defender un modelo de informe que determina el alcance ético apropiado del proceso de asesoramiento genético para la comunicación de hallazgos incidentales al cual llamo "modelo iterativo" para resaltar la continuidad del proceso de consentimiento informado

entre el consejero y el participante de la investigación. Para ello, las teorías de consentimiento informado serán analizadas y adaptadas al caso de la investigación en salud humana con procedimientos de secuenciación de genoma/exoma completo. Además, valores relevantes a la ética de la investigación y características de los datos genómicos serán tomados en consideración. El modelo iterativo de consentimiento informado se basa en los modelos de consentimiento informado tradicional y dinámico, para asegurar la comprensión y la elección autónoma por parte de los sujetos de la investigación.

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# Contents

# Chapter 1. Introduction

## 1. General Introduction

There is an ongoing discussion in the literature, legal and ethical committees world-wide addressing the disclosure of incidental findings in whole genome sequencing (WGS)/whole exome sequencing (WES) research. Facing the rapid acceleration of WGS/WES technology development and their practical implementation in research and clinical routine, there is an urgent need to develop and define ethical and legal standards for informed consent and disclosure of incidental findings.

Even though the US national bioethics advisory commission (NBAC) favored the model not to return incidental research findings in 1999, several organizations and advisory commissions complemented guidelines suggested over time that research individuals should be offered to learn about incidental findings that can affect their health outcome (Wolf et al. 2012, Bradbury, McCormick and Robson 2014). Among others, the institutions that most recently developed specific recommendations for the report of incidental findings in the context of WGS/WES are the American College of Medical Genetics and Genomics (ACMG) and the US Presidential Commission for the study of bioethical issues in 2013. Moreover, topics like share of decision making between research providers and participants or the right to reject receipt of incidental findings are addressed in these guideline documents (Presidential Commission 2013).

Informed consent is a major requirement in clinical research and applies to the setting of research studies involving humans and using WGS/WES procedures. In the course of history, informed consent was more and more refined and adapted to specific settings, in particular to research studies. However, due to the broadened implementation of new technologies in clinical research, as WGS/WES, the informed consent requirement needs to be adapted to the technological challenges and specific ethical problems that arise in this context (Presidential Commission 2012).

Especially in the new field of genetic counseling and whole genome data collection, it is always dealt with the delicate topic of racism, discrimination, and eugenics that showed us in recent history the possible consequences of missing autonomy. A first intuition that I will defend in this dissertation is that the disclosure genetic data demands comprehensive counseling process prior to consenting, as it is linked to very personal, predictive and determinative data.

Several informed consent models have been developed to address the ethical needs in the setting of

clinical research with WGS/WES data and the return of research results. However, facing the problems that arise in their concepts and practical application, there is still space for improvement, especially with regard to the information process and guided communication transmission of research results. Ideally, a consent model has to be compatible with various aims in research and public health and with individual well-being which can be sometimes discordant.

The objective of the thesis, which will be developed in full detail in Chapter 4, is to develop and describe an informed consent model –"the iterative feedback model"– for potential participants in human health research studies using whole genome sequencing (WGS)/whole exome sequencing (WES) procedures, and for the disclosure of incidental findings after the enrollment in a research study. I will defend a model that supports and puts emphasis on the communicative process with the research participant, a crucial component of the informed consent process. Even though there will be objections discussed at the end of chapter 4, the model tries to outpace defects of other models that will be described in the course of chapter 4. The hypothesis is that the iterative feedback model fits better than the alternative models the ethical framework containing generally accepted ethical principles of research ethics and the specific characteristics of WGS/WES data.

Guidelines by the US Presidential Commission for the study of biomedical issues (2013), the paper "A Framework for Analyzing the Ethics of Disclosing Genetic Research Findings" by Eckstein et al. (2014), as well as the paper "Models of Consent to Return of Incidental Findings in Genomic Research" by Appelbaum et al. (2014) are selected literature for this work. The US Presidential Commission for the study of bioethical issues is an advisory panel of physicians, scientists, ethicists, lawyers, engineers, and theologians that advises the president on bioethical issues in the fields of biomedicine, science and technology (Presidential Commission 2012&2013). In this thesis, it will be referred to the Commission's guidelines in various paragraphs in view of the Commission's strong lead on guidelines addressing the return of findings and ethical issues arising as a result of the rapid progress of WGS/WES technologies. In particular, the guideline document "Anticipate and Communicate. Ethical Management of Incidental and Secondary Findings in the Clinical, Research, and Direct-to-Consumer Context" (2013) will contribute to the clarification of the terminology for research findings. In this regard, the paper "A Framework for Analyzing the Ethics of Disclosing Genetic Research Findings" by Eckstein et al. (2014) offers another approach for the classification of research findings and explains which criteria findings must meet in order to be revealed to research subjects. Eventually, the paper "Models of Consent to Return of Incidental Findings in Genomic Research" by Appelbaum et al. (2014) outlines informed consent models for the feedback of incidental findings which are commonly found in the literature. The authors give an ethical eval-

uation of the models by using the criterion "researchers' ethical obligation" and point out advantages and disadvantages of the models regarding the criterion of "practicality". I will incorporate this approach by applying the ethical principles that will be mapped out in the theoretical framework to these informed consent models.

## 2. General and specific aims

The general aim of the thesis is to develop an ethical framework for an informed consent model for the disclosure of incidental findings in the setting of whole genome sequencing (WGS)/whole exome sequencing (WES) research with human research individuals.

In the course of the thesis, several informed consent models will be analyzed and furthermore challenged by applying ethical principles. As mentioned, it will be taken into account that a consent model has to be compatible with principles and values in research and public health, as well as with the research individual's well-being and rights. Since a consent model never fits all of the proposed interests, the thesis' aim is to carefully weigh every suggested reasonable position. The ethical analysis of the informed consent models is supposed to guide the reader towards the "iterative feedback model", a model incorporating already existing consent theories by simultaneously covering crucial ethically demanded principles. Thus, the ethical analysis demonstrates why the "iterative model" fits best the demands of overarching ethical principles among the analyzed informed consent models for research studies using WGS/WES procedures. Another important aim of the thesis is to point out the strengths and weaknesses of the "iterative feedback model".

After having outlined the general aim and idea of the thesis, the more specific aims as well as the more detailed proceeding will be presented.

The first specific aim of Chapter 2 and 3 is to picture biological theories, technology, statistical evaluation of genetic tests and the history of informed consent theories, as well as legal aspects of informed consent and the disclosure of research findings in the United States. This background knowledge should help the reader to understand why ethical issues arise when considering the case of research studies involving human subjects and using WGS/WES procedures.

Subsequently, chapter 4 addresses the development of an ethical framework for the disclosure of incidental findings in research studies using WGS/WES procedures by evaluating ethical theories for informed consent, by highlighting crucial ethical principles in this context, and by evaluating the particular importance of each principle. Furthermore, a paragraph will be dedicated to outline the characteristics of WGS/WES data and the return of findings to research participants. This should be considered a supportive tool to point out the specificity of WGS/WES research and to design of the

iterative feedback model. Also, introducing a genome wide association study (the rare diseases genomes project) as case is supposed to help the understanding of ethical issues and questions in this context.

Moreover, the theoretical framework of chapter 4 tries to give valuable definitions on terms connected to the ethical analysis of research studies using WGS/WES technologies. One section is fully dedicated to clarify and re-define the terminology of research findings, incidental findings, secondary findings etc. Also, one of the aims is to clearly set the conditions when findings should be disclosed to participant regarding the vast amount of data generated by WGS/WES.

Taking into account the developed ethical and terminological framework, current informed consent theories applied to the context of research studies using WGS/WES procedures and the disclosure of incidental findings will be introduced and evaluated. Advantages and disadvantages of each model will be outlined. Facing the main benefits and problems after the evaluation, an alternative model will be presented – "the iterative model" - based on the strengths and weaknesses worked out before. In the further course of the thesis, the "counselling process" will be described, a crucial characteristic of the iterative feedback model.
Finally, the main challenges arising in the context of the implementation of this model will be presented and discussed.

# Chapter 2: Scientific background of genetics and whole genome/whole exome sequencing

## 1. Introduction

The objective of this chapter is to introduce the main terminology of biological processes related to genetics. I will introduce several definitions on genetics in general and DNA formation, translation and transcription in particular. Moreover, an essential paragraph will be dedicated to define mutations and to classify them – with regard to genetic tests and the detection of genetic aberrations.

A crucial paragraph will describe technical reliability of genetic tests and what to consider when statistical risks derived from whole populations or cohorts are transferred to single individuals.

Based on the overview on biological processes and genetic tests, the chapter also depicts how sequencing technologies have evolved and how they could develop in the near future. Furthermore, this chapter addresses the application range of genetic sequencing and gives a short outlook on bioinformatics supporting the implementation of whole genome/whole exome sequencing in clinical routine and research.

## 2. Genetics

"Genetics" is a subfield of biology addressing the transfer of hereditary dispositions to next generations of particular cells or to an organism. In contrast, "epigenetics" investigates the activity of such hereditary dispositions in different tissues, as well as mechanisms controlling those activities. The "genotype" is the totality of genetic dispositions regarding a whole organism, while the "phenotype" refers to characteristics that appear in an organism, including anatomical, physiological, biochemical, epigenetic and (in complex organisms) psychological characteristics during its life-span (Deutscher Ethikrat 2013:8).

In the following sections, the composition of the genetic code, as well as its translation into proteins which play a major role in the physiology and biochemical processes of an organism will be described. The basic aspects of the genome, its transcription into RNA and its translation into proteins, is outlined in Figure 1.

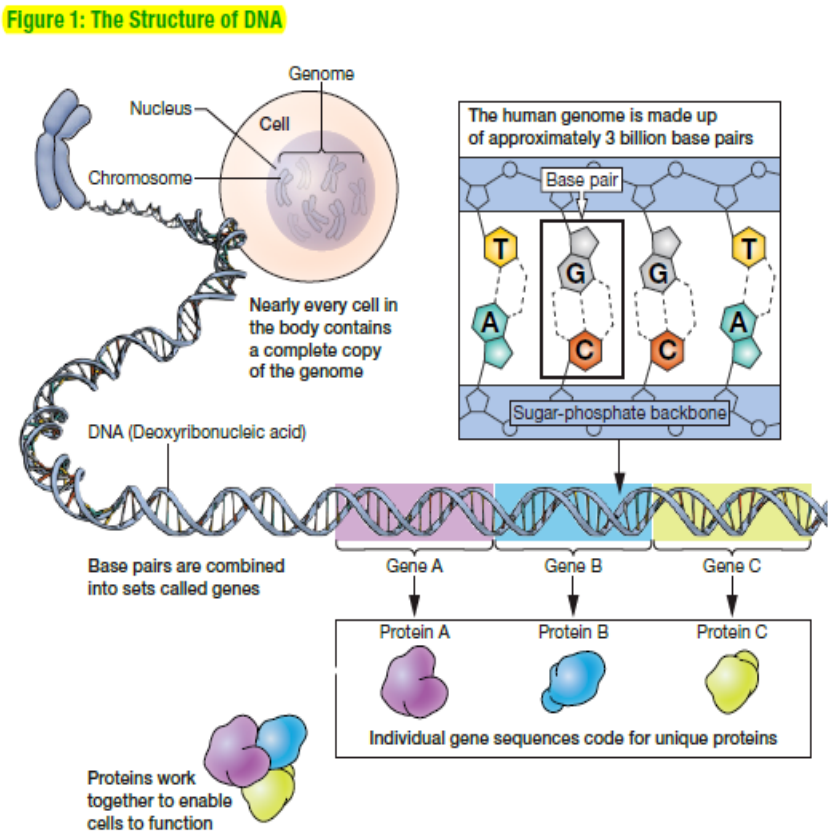



Figure 1: "The structure of DNA", Source: Presidential Commission (2012:17).

## 2.1. Components building the genetic code

DNA is a double stranded nucleic acid molecule in an alpha-double helix consisting of two anti-parallel nucleotide strands. DNA is composed of four different nucleotides which repetitively build up the genetic code (Murken et al. 2006:2, Figure 1: "The structure of DNA").

There is a general distinction between nucleotide acids: desoxyribonucleotide acid (DNA) and ribonucleotide acid (RNA). Both types of nucleotide acids are polymers of nucleotides that are polymerized by pyrophosphate segregation of nucleoside tri-phosphates. Each nucleoside mono-phosphate consists of an organic base, sugar and phosphoric acid. Those highly energetic nucleoside tri-phosphates build the basis for the synthesis of nucleotide acids, namely Adenine (A), Guanine (G), Cytosine (C) and Thymine (T). The nucleotides are complementary, binding to each other via the formation of hydrogen bonds: Adenine is complementary to Guanine, whereas Cytosine pairs off Thymine in DNA and with Uracil in RNA. The sugar used for DNA synthesis is pentose 2'desoxyribose, while RNA is made of ribose. Furthermore, the base Thymine is replaced by Uracile (U) in RNA (Lister Hill National Center for Biomedical Communications 2015:9).

The 3'-OH-group of the sugar molecule and the 5' phosphate acid group indicate a "direction" in the DNA molecule. The alpha-helix is stabilized by intermolecular forces (bonds between the complementary bases of the anti-parallel helix), and intramolecular forces (hydrogen bonds between helices, and so called stacking-interactions. In contrast, RNA is a single stranded molecule and can build intramolecular helical structures (Murken et al. 2006:1-6).

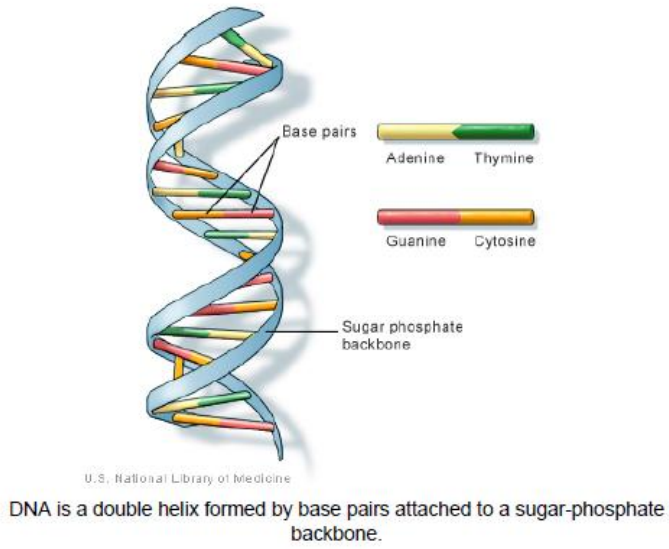



Figure 2: "The components of DNA", Source: Lister Hill National Center for Biomedical Communications (2015:10)

## 2.2. The human genome

DNA is the carrier of genetic information. Genes are DNA sections that usually code for a particular gene product (RNA, protein).

DNA of eukaryotes is arranged in a complex of DNA and histones and non-histone-proteins, which is called chromatin. Humans have 23 chromosomes, each consisting of two chromatid strands, either in a haploid (gamete and spermatozoon), or in a diploid chromosome set (other somatic cells). Segments of DNA are "genes" coding for proteins that can be translated and transcribed and regulate body functions (Harden 2010). During the "interphase" of the cell cycle, chromosomes are uncoiled. Thus, microscopic pictures showing the characteristic shape of chromosomes are taken during the "metaphase" (Murken et al. 2006:9).

The sequence of bases composes the genetic code. Each amino acid is coded by a triplet of base pairs. This code is degenerated, meaning that there are more coding possibilities than necessary and most of the amino acids are coded by more than one particular composition of the triplet. The code is universal in all living beings (and viruses), comma free and non-overlapping. The AUG-triplet

generally serves as start-codon, coding for the amino acid Methionine (Murken et al. 2006:8-9).

The biggest amount of DNA is located in the nucleus of a cell. In addition, there is DNA stored in mitochondria which are located in the cytoplasm (Murken et al. 2006:9-10).

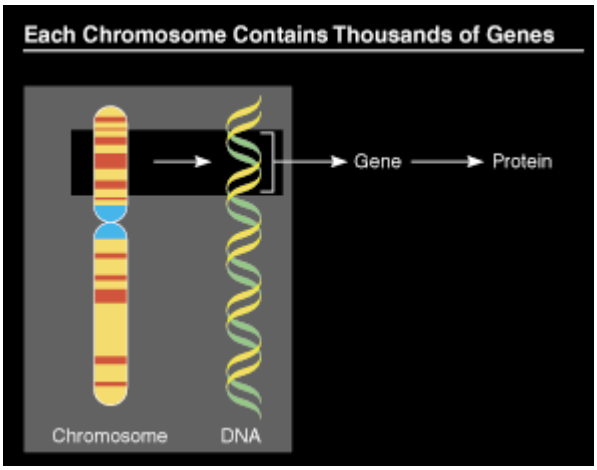



Figure 3: "The central dogma of molecular biology: DNA codes for proteins"
Source: National Institutes of Health (2015).

The human genome comprises 3 billion base pairs, although only 1.1% of the DNA contained in cells can be considered as coding regions (Lister Hill National Center for Biomedical Communications 2015: 13). There are about 25.000 genes coding for proteins. Since coding mRNA and proteins are further modified by posttranscriptional and posttranslational mechanisms, each gene can code for various different proteins. As a result the number of proteins found in the cell exceeds the number of genes (Murken et al. 2006: 12). Genes are composed of coding regions ("exons", ca. 1.1%) interrupted by non-coding regions ("introns", ca. 24% of the genome). The remaining 75% of DNA consists of "intergenic" DNA – non-coding DNA between the transcribed units (MeSH Database Definitions 2015). The function of these non-coding sequences is currently intensively studied as there is a huge number of RNA molecules which are not involved in protein synthesis. The ENCODE project (Encyclopedia of DNA elements) investigating all functional elements of the human genome, suggests that at least 80 percent of the non-coding DNA (e.g. microRNAs, siRNAs, snRNAs) plays an essential role in the system of epigenetic gene regulation (Ecker et al. 2012, The ENCODE Project Consortium 2012).

Main mechanisms of epigenetics are the modification of histones which wrap the DNA molecule. Likewise, gene products, as RNA and other proteins, can influence the reading process of DNA. In this way, epigenetic modifications determine when and where in a cell genes are expressed. Epigenetic modifications can be acquired, e.g. due to psychological stress, or environmental modifications, which can last for variable time periods. Some of these can be inherited, others are

short term modifications, regulating for instance the amount of gene products (transcription factors, repression factors), metabolism products, or hormones as needed for the cellular function in a given setting (Deutscher Ethikrat 2013: 11-13).

Introns and exons are transcribed into messenger RNA (mRNA) (which will be explained in more detail in the following paragraph, compare also Figure 2 "The central dogma of molecular biology"). However, in a further step the splicing apparatus removes the introns from mRNA implying that only exons are translated into the end products – proteins. The so called "promoter regions" regulate the transcription process by giving the start signal via characteristic sequences as TATA or CAAT. "Regulatory sequences", which are located near the genes, have the ability to bind proteins involved in the transcription process and interact with the promoter region and the RNA-polymerase. Eventually, "spacer sequences" are responsible for the position of regulatory sequences, and thus, for their further interaction with the promoter regions (Murken et al 2006:11-15).

The human genome also exhibits repetitive sequences. Among these sequences, most of the regions still remain without or with unknown function (Murken et al. 2006:12).

### 2.2.1. Replication of DNA

During each cell division, genetic information is transmitted to the daughter cells. In order to divide, a cell must duplicate its genetic information, a process called replication. Replication takes place during the "S-phase" of the cell cycle and can be described as a "semi-conservative" process: the DNA double helix is uncoiled and both strands provide a template for the formation of new DNA strands. Hence, the chromatid contained in each chromosome is duplicated into two chromatids (Lister Hill National Center for Biomedical Communications 2015:29, Figure 4: "Mitosis and meiosis")

The division of body cells is depicted on the right. During meiosis, DNA replicates and is transferred to the daughter cells. In contrast to mitosis, meiosis (the cell division creating egg and sperm cells) is a two-step process that reduces the number of chromosomes by half (as only 23 chromosomes are inherited from each mother and father).

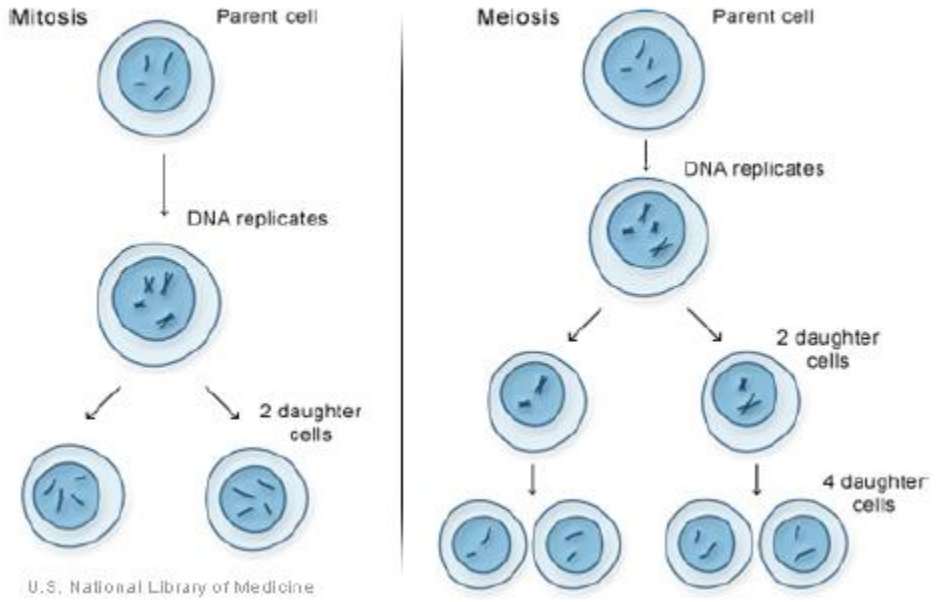



Figure 4: “Mitosis and meiosis”, Source: Lister Hill National Center for Biomedical Communication (2015:29)

### 2.2.2. Transcription

The “translation” of genetic information into proteins is initiated by the transcription process. During this process, necessary components for the translation into proteins are synthesized, namely rRNA of the ribosomes, transportation units for the amino acids (tRNA molecules), and mRNA coding for proteins. The transcription is carried out by RNA-polymerases and takes place in the nucleus of eukaryotic cells (Lister Hill National Center for Biomedical Communications 2015:24). The reading process of DNA is carried out only at one stand of the double helix, the so called “coding strand”, from the 3’ to the 5’ end. The read out sequence is controlled by promoter sequences, each corresponding to a particular gene. The promoter is the starting point where transcription begins and where it is regulated. In contrast to prokaryotic RNA-polymerases, eukaryotic RNA-Polymerases are not able to initiate the transcription process by themselves. So called “transcription factors” start the transcription process by accumulating at the promoter sites. Eventually, the RNA-polymerase is phosphorylated which triggers its release from the initiation complex and starts the mRNA synthesis. The transcription process is stopped by the signal of “palindromic nucleotide sequence” of the DNA. Such “palindromic base pairs” lead to a loop in the RNA structure and signal the termination of mRNA synthesis (Murken 2006:21-22).

### 2.2.3. Posttranscriptional modification of mRNA

In contrast to DNA-polymerases, RNA-polymerases do not show proofreading activity due to the

vast amount of mRNA transcribed and released to the cytoplasm, and due to a high tolerance for single non-functional proteins. One of the most important posttranscriptional processes to mention is the splicing mechanism. In a complex splicing and synthesis process of gene products, transcribed introns are removed (spliced). The so called "spliceosome" tags intron-exon transitions and splices the mRNA sequence at the indicated loci. Furthermore, the nucleotide sequences of exons are merged and transported to the cytoplasm (Murken et al. 2006:24). Alternative splicing refers to the possibility of keeping facultative introns in the "mature" mRNA sequence which is transported to the ribosomes. Hence, alternative splicing –the different combination possibilities of introns and exons– lead to different gene products. In consequence, the number of functionally different gene products clearly exceeds the number of genes contained in the DNA sequence (Murken et al. 2006:22-25).

### 2.2.4. Transcriptional regulation

Eukaryotes regulate genes individually. Gen regulatory proteins can bind to particular DNA regions tagged by binding motives, such as the "helix-turn-helix", "homeodomains", or "TATA-boxes". These regions can interact with transcription factors and the RNA-polymerase II and thus control the transcription mechanism (Murken 2006:25). Moreover, specific proteins that bind at these regions are able to either enhance or to silence genes by controlling the RNA-polymerase activity. Alternative splicing can serve as a regulatory mechanism, regarding the selectivity of genetic information that is transcribed. Likewise, the methylation of cytosine rests of CpG (Cytosine-Guanine) islands influences the gene expression. Increased methylation goes hand in hand with a reduced gene expression of the gene behind the methylated region (Murken et al. 2006:26).

### 2.2.5. Translation

The translation of mRNA into proteins is carried out at the ribosomes whose subunits are located in the cytoplasm. The translational mechanism is subdivided into initiation, elongation and termination. In order to initiate translation, an initiation complex is formed, consisting of mRNA, initiation proteins, the small ribosomal subunit, and initiator tRNA (Lister Hill National Center for Biomedical Communications 2015:24).

During the elongation process, mRNA is read out in triplets from the 5' to the 3' end. tRNA molecules carry amino acids which bind to free triplets of the mRNA. Meanwhile, elongation factors support the binding process. The elongation mechanism is continued until the stop codon is reached (there is no charged tRNA molecule corresponding to the stop codon). Eventually, binding

“release factors” trigger the liberation of the synthesized protein and the decomposition of the ribosome to its subunits (Murken et al. 2006:30).

### 2.2.6. Posttranslational modification of proteins

The functionality of proteins can be achieved directly after their synthesis. Nonetheless, it is also possible that full functionality needs further modification.
For instance, the activation of proteins can be regulated by “exo-“ or “endopeptidases”, or by adding functional groups such as carbohydrates. Furthermore, a common mechanism to activate proteins is phosphorylation executed by protein kinases, as well as the acetylation or methylation of proteins (Murken et al. 2006:32-34).

## 2.3. Mutations

The information of the DNA is subject to permanent changes, so called “mutations”. Single bases, as well as whole sequences can be exchanged, deleted, duplicated, or inserted at different genetic loci through the mutation process:
The majority of genetic diversity is based on single nucleotide polymorphisms (SNPs). Two related human genomes differ in every thousandth base pair on average. Approximately 60.000 SNPs are located in coding regions of the genome. DNA-copy variants, as deletions and duplications of DNA sequences, can lead to modifications in the genome. Furthermore, differences in the repetition of sequences contribute to the variability of the genome (Murken et al. 2006:14-15).

In the context of evolution, mutations remain if they improve surviving abilities for the organism in a given environmental setting. Mutations that imply a disadvantage for the organism underlay negative selection and cannot be established over several generations.

Mutations of genes lead to the formation of so called “alleles”, different variants of a certain gene, which are located at the same genetic locus of homologue chromosomes. There are many different alleles found in a population. However, an individual has only 2 alleles due to its diploid chromosome set. In case of identical alleles, the gene is called “homozygote”, whereas two different alleles are “heterozygote” by definition.
Genetic variability develops due to random combinations of different alleles inherited from the parents. Thus, a mutation is any genetic aberration in the DNA sequence which changes the sequence from a normal allele prevalent in the population to an abnormal or rare variant. A

“polymorphism” is a variation of DNA sequence which is common in the population. The threshold set between a mutation and a polymorphism refers to an incidence of 1% or more in the population. If the frequency of a genetic aberration is lower than this cut-off point, the altered allele is regarded as a mutation (Twyman 2003).
There are also other mechanisms, as epigenetic modifications, contributing to the phenotypic and genotypic individuality of organisms (Murken et al. 2006:14-15).

Mutations can either be inherited (so called “germ line mutations”) or acquired (“somatic mutations”), which can be spontaneous, i.e. random, or a result of environmental mutagens, e.g. in cigarette smoke. In contrast to germ line mutations, somatic mutations are located in a limited number of somatic cells and do not show inheritance patterns (Lister Hill National Center for Biomedical Communications 2015:39). An example for a germ line mutation in breast cancer patients are genetic modifications of the BRCA1/2 genes, whereas a common somatic mutation in cancer affects the p52 gene. Most of the observed mutations are the result of events, such as DNA-replication errors, or recombination errors (cross-over-errors during meiosis). Furthermore, other causes of mutations, as the effect of chemicals, or radiation induced modification of nucleotide acids have been extensively studied (Murken et al. 2006:58; 63).

Not all genetic modifications, as already explained, cause disadvantages for an individual. However, just a small percentage of mutations have a positive effect leading to a better adaptation to the living conditions of an organism. Moreover, some genetic aberrations alter a gene’s DNA sequence but do not change the function of the protein coded by the gene. Additionally, potentially harmful gene mutations are often repaired by enzymes before the gene is expressed and an altered protein made (Lister Hill National Center for Biomedical Communications 2015:45). Each cell has pathways through which DNA can be repaired and which protect the body from many genetic alterations caused by defective transcription or translation.

The human genetic code is able to bear a large number of mutations without effects on health, since many pathways are protected by “alternative pathways”, achieving the same functionality with different molecular interactions. This can complicate diagnosing genetic conditions (the correlation of genetic aberrations with phenotypic changes) difficult. For instance, there can be a lack of clarity if a mutation is directly involved in the development of an unfavorable clinical condition; these genetic changes are called “variants of unknown significance (VOUS)”. VOUS often occur in the context of mutations at genetic loci which are not located in the suspected disease-related genes (Lister Hill National Center for Biomedical Communications 2015: 45). Anticipating the case study

(the "rare diseases genomes project") that will be introduced in chapter four, in rare diseases there is frequently a lack of evidence for disease-causing variants due to limited data availability.

### 2.3.1. Classification of Mutations

Mutations can be classified into "genome mutations" (a changed number of chromosomes), "chromosome mutations" (aberrations of a huge part of the chromosome), and "gene mutations" (single aberrations of one or more nucleotides in a particular chromosome).
Regarding genome mutations, a change in the number of chromosomes is subsumed under the term "aneuploidy". Deletions, insertions, duplications of chromosomal areas, translocations, and inversions are possible mutational aberrations of chromosomes. Gene mutations include point mutations as substitutions, deletions and insertions of single nucleotides. Furthermore, mutations can consist of large-scale deletions and insertions of several kilo-bases or mega-bases (Murken et al. 2006:42-43).

Mutations are distinguished according to the locus of the mutation in the gene: mutations in the coding region ("silent mutations", "missense mutations", "nonsense mutations"), "frameshift mutations", mutations in the promoter, in the splicing region or mutations of polyadenylated regions and of the Cap-site (Lister Hill National Center for Biomedical Communications 2015:43-44).
Silent mutations code for the same amino acid (no protein change), missense mutations cause an amino acid change, and nonsense-mutations code for a stop-codon. Mutations causing a shift of the read out bases via a deletion or an insertion in the coding region of a gene are called frameshift mutations. If single nucleotides are mutated in the promoter region (promoter mutation), the expression of the gene is either up or down regulated. Furthermore, there are certain sequence motives in transition regions of exons and introns which are needed to initiate the splicing mechanisms. Mutations in those motives can hamper or change the splicing process. Likewise, polyadenylation of mRNA is necessary for the export of mRNA from the nucleus to the cytoplasm. Mutations of the polyadenylated regions can lead to less mRNA transportation or even stop the export completely (Murken et al. 2006:49).

## 2.4. Diagnostic, prognostic and predictive genetic analysis

Number and microscopic structure of the chromosomes, the sequence of the DNA, or the sequence of genetic products, as RNA, can be investigated via a genetic analysis. Thus, the genetic analysis can comprehend the analysis of single genetic loci or genome wide screening for genetic aberrations.

In contrast to other laboratory tests, a genetic analysis reveals a sequence of nucleotides (Lister Hill National Center of Biomedical Communications 2015:117). Hence, determining the amount of the DNA molecule is not within the scope of a genetic analysis.

The result of a genetic analysis only shows clinical significance if the genetic variation implies a changed phenotype. Without the correlation between phenotype and genotype, genetic analysis cannot be used in terms of a clinical examination.

In a clinical context, genetic analysis is used to diagnose germ line or acquired genetic aberrations that cause or can cause pathogenicity. For instance, cancer cells show acquired mutations in either oncogenes or tumor suppressor genes which can be revealed by a genetic analysis. This analysis can give predictive (e.g. therapeutic response) and/or prognostic (survival probability) information about the course of the disease or adequate therapeutic options. In contrast, predictive genetic diagnostics cannot be correlated to a yet visible phenotype, as disease or as functional impairments. The test aims for the prediction of future phenotypic changes, e.g. disease, by indicating a probability for future phenotypic alteration (Deutscher Ethikrat 2013:13-14).

### 2.4.1. Effects of genetic dispositions on health and life

Genes play an important role in organisms regulating physiological and biochemical functions which depend on the frequency of reading out genes and translating them into RNA products. Furthermore, an organism always keeps certain equilibria of physiological and biochemical processes depending on sex, age, nutrition, life style and other external conditions. In this regard, the mere coexistence of genetic variants (genotype) and a phenotypic characteristic of an individual can be considered coincidental. Statistical validation associates a genetic variant with phenotypic characteristics by studying whole populations. However, molecular or cell biological evidence is needed to confirm a cause-effect relation between genetic variant and phenotypic characteristic (Deutscher Ethikrat 2013:14).

In some cases, a single aberration in the genotype can trigger a change in phenotypic characteristics, especially at the time when the functional impairment is due to a defect of a protein coded by the gene. For instance, carriers of a mutation in BRCA1/2 genes show defects in BRCA1/2 proteins which are essential to prevent breast and ovarian cancer due to their participation in a pathway that mediates error-free repair of DNA double strand breaks by homologous recombination (Friedenson, 2007).

A mutation localized in a single gene and correlated with a high risk of disease development, disabilities or developmental disorders, is called a “monogenic” cause of disease. Such mutations

can be results of different patterns of inheritance (recessive or dominant) (Deutscher Ethikrat 2013:19-20).

In contrast to monogenetic causes, multi-factorial diseases are caused by more than one external factor (environmental conditions, nutrition, life style, side effects of medication) and/or genetic dispositions. For instance, arteriosclerosis, heart attacks, obesity, or diabetes type II can be considered multi-factorially caused diseases. These diseases are associated with complex genetic constellations and an even more complex phenotype. Therefore, it is difficult to extrapolate a clear cause-effect mechanism associating genetic dispositions and phenotypic characteristics. Since the development of a disease is constituted by genetic, epigenetic and environmental factors, it is more appropriate to call the corresponding genetic variants polymorphisms instead of (pathogenic) mutations (Lister Hill National Commission for Biomedical Communications 2015:68-69).

Chromosomal aberrations can cause disorders which can lead to massive damage, even in the prenatal fetus. The range of chromosomal disorders comprises lethal disorders at an early embryonic stage (e.g. autosomal monosomies, polysomies etc.), as well as aneuploidies or hyperdiploidies (e.g. trisomy 21) which do not strongly affect the viability of a fetus (Deutscher Ethikrat 2013:25-27).

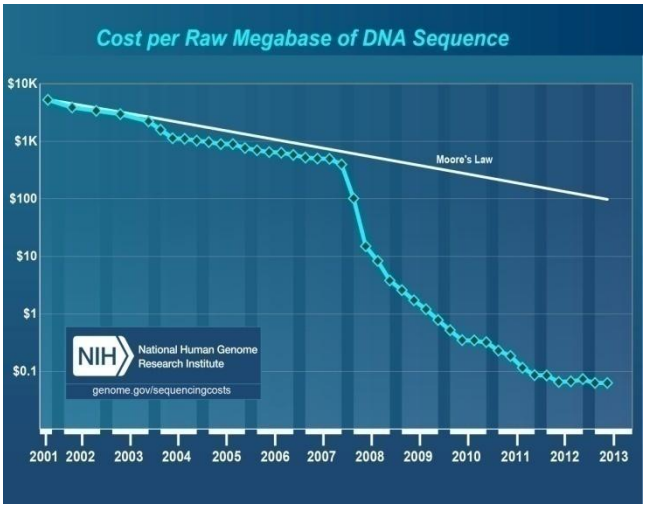
In consideration of genetic aberrations and their effects on the phenotype of an organism, it has been presented how genetic dispositions and external factors can affect an individuals' health. Moreover, it has been stated how genetic tests can be used to diagnose or to predict a current or future health state. In the next section, the focus will be on the development and state of the art knowledge of genetic diagnostics and research technologies.

## 3. State of the art knowledge: genetic diagnostics and research technologies

High-throughput sequencing technologies have revolutionized genome analysis and consequently genetic diagnostics possibilities, not least because of the enormous technological shift during the last decade and due to dramatically dropping costs per sequenced base of raw sequence (Niedringhaus et al. 2011). Also, advances in bioinformatics go hand in hand with the development of sequencing technologies (Deutscher Ethikrat 2013:32). Efforts in sequencing cost reduction and genome wide analysis paved the way for groundbreaking insights into complex diseases. This development supports research on genetically caused diseases which requires a huge amount of genomic data in order to investigate genotype-phenotype relationships clinical and therapeutic

research could take advantage of (Deutscher Ethikrar 2013:32-34).

Figure 5a/b shows the significant cost reduction in sequencing technologies depicting the "cost per megabase of DNA sequencing" as well as the "cost per genome" (National Human Genome Research Institute 2015).



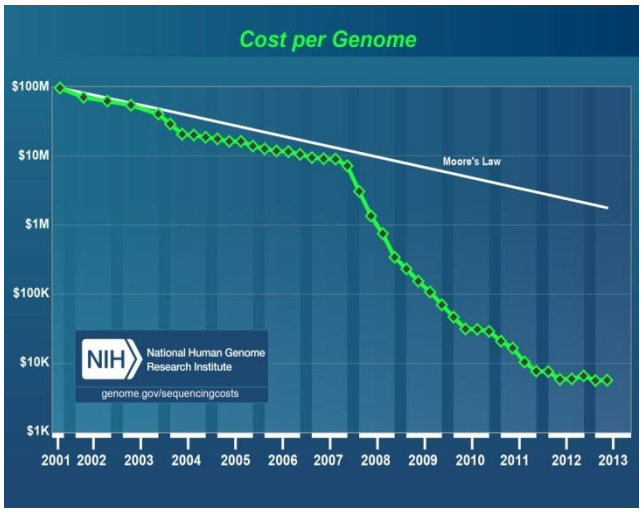




Figure 5a: "Costs per raw Megabase of DNA sequence" Figure 5b: "Cost per Genome"

Source: National Human Genome Research Institute (2015)

Regarding the two graphs, the costs are accounted for: laboratory, administration, sequencing instruments and related large equipment, information management systems, shotgun library construction. Not reflected costs are: quality assessment/control for sequencing projects, development of bioinformatics, informatics equipment, data analysis (e.g. indentifying variants, interpretation of results).

The graphs do not only depict the quickly dropping sequencing costs, but also show curves of Moore's law – a hypothetical curve (depicted on a logarithmic scale) which describes long-term trends in the computer hardware industry that amounts to the doubling of "compute power" every two years. Technologies that are able to maintain the innovation rate of Moore's Law are considered outstanding developments (National Human Genome Research Institute 2015).

In 2008, the implementation of so called "second generation sequencing" or "next generation sequencing" (NGS) technologies, high-throughput technologies led by Illumina, Roche and Life Technologies, was launched. Sanger-based sequencing (dideoxy chain termination sequencing) was

then replaced by more innovative NGS methods which have the capacity to sequence a large quantity of DNA fragments simultaneously. This resulted in a tremendous break-through in sequencing cost and time reduction (National Institute of Human Genome Research 2015). Due to the introduction of next generation sequencing technologies, it will be possible to sequence a whole human genome for approximately 1.000 US-Dollar in the next 5-10 years (Deutscher Ethikrat 2013:33; Mardis 2011). Regarding the rapidly dropping price of whole genome sequencing (WGS), it is rather convenient to sequence whole genomes instead of performing discrete genetic tests (Presidential Commission 2012:30). Sequencing the coding exons (whole exome sequencing, WES), composing the "exome" (the exome only makes up 1% of the whole genome with approximately 4.6 billion base pairs), needs less data retention while showing higher data quality. However, it should be taken into consideration that there still remains the difficulty of data interpretation. For instance, raw sequences need to be evaluated; data has to be harmonized consistently and compared with references, and unknown variants have to be identified. Eventually, the "1000 dollar genome" converts into a "100.000 dollar interpretome" (Perkel 2013). Although advanced interpretation and reporting software is undergoing rapid development, Perkel (2013) claims that from a clinical point of view, automated steps are not sufficient to identify variants underlying special phenotypes or human diseases.

Nevertheless, the price per sequenced genome strongly depends on the degree of capacity utilization. Furthermore, data interpretation tools are developing and improving, just as data bases containing genome-phenotype-profiles grow. Hence, it can be assumed that the development of new algorithms for data analysis is just a matter of time (Deutscher Ethikrat 2013:33).

## 3.1. From First to Next Generation Sequencing

DNA sequencing was pioneered by Sanger and Coulson who developed the chain termination method in 1975 together with Maxam and Gilbert who came up with a method of chemical DNA modification in 1976-1977. In 1977, Sanger sequenced the first genome of the bacteriophage phi X 174, which contains 5375 base pairs in length (Niedringhaus et al. 2011). In the mid 1980s semi-automated DNA platforms were developed, followed up by more cost-effective nucleases, polymerases, more rapid template preparation etc. (Slatko et al. 2011).

Two principles of genetic analysis dominate genetic sequencing in human beings: the hybridization of oligo-nucleotides and the polymerase-chain-reaction (PCR) (Deutscher Ethikrat 2013:30).
Since the 1990s, the DNA sequencing market has been almost exclusively dominated by capillary-

based, semi-automated machines based on the Sanger method (primary offered by Applied Biosystems, then integrated into Life Technologies and Beckman Coulter) (Niedringhaus et al. 2011). Regarding this method, DNA can be prepared in two ways. For shotgun de novo sequencing, randomly fragmented DNA is cloned and subsequently transferred into Escherichia coli (cf. Figure 6a). "Shotgun" means to enzymatically fragment DNA and sequence the fragmented strands (Schlebusch and Illing 2012). For targeted re-sequencing, a PCR is performed with primers delineating the target gene sections. Consequently, either many clonal copies of a single plasmid in a bacterial colony or PCR amplicons in a single reaction volume can be picked as an amplified template. The sequencing reaction takes place in a "cycle sequencing" reaction, in which cycles of template denaturation, primer annealing and primer extension are performed. Each round of primer extension can be stochastically stopped by the integration of fluorescently labeled dideoxynucleotides (ddNTPs). As a result, the label of the terminating ddNTP of DNA fragments matches the nucleotide identity of the final position (Shendure and Hannlee 2008). When the extended DNA fragments are subsequently ordered according to their lengths, the sequence can be read out, assuming that every length appears at least once due to the statistical break off at any possible position in the PCR extension phase. Thus, the labeled nucleotides and the order of their sequence can be made visible, up to sequences of around 1.000 base pairs.

Since the 1980s, the Sanger method got more and more elaborated not only by the development of an optical detection of ddNTPs labeled fragments, but also by the introduction of capillary electrophoresis to read out the detected sequences, which led to a fully automated sequencing system. After further improvements in the 2000s, Sanger sequencing costs approximately 0.50 dollar per kilobase. However, there are NGS methods which enable sequencing costs per megabase under 0.1 dollars (Shendure and Hanlee, 2008).

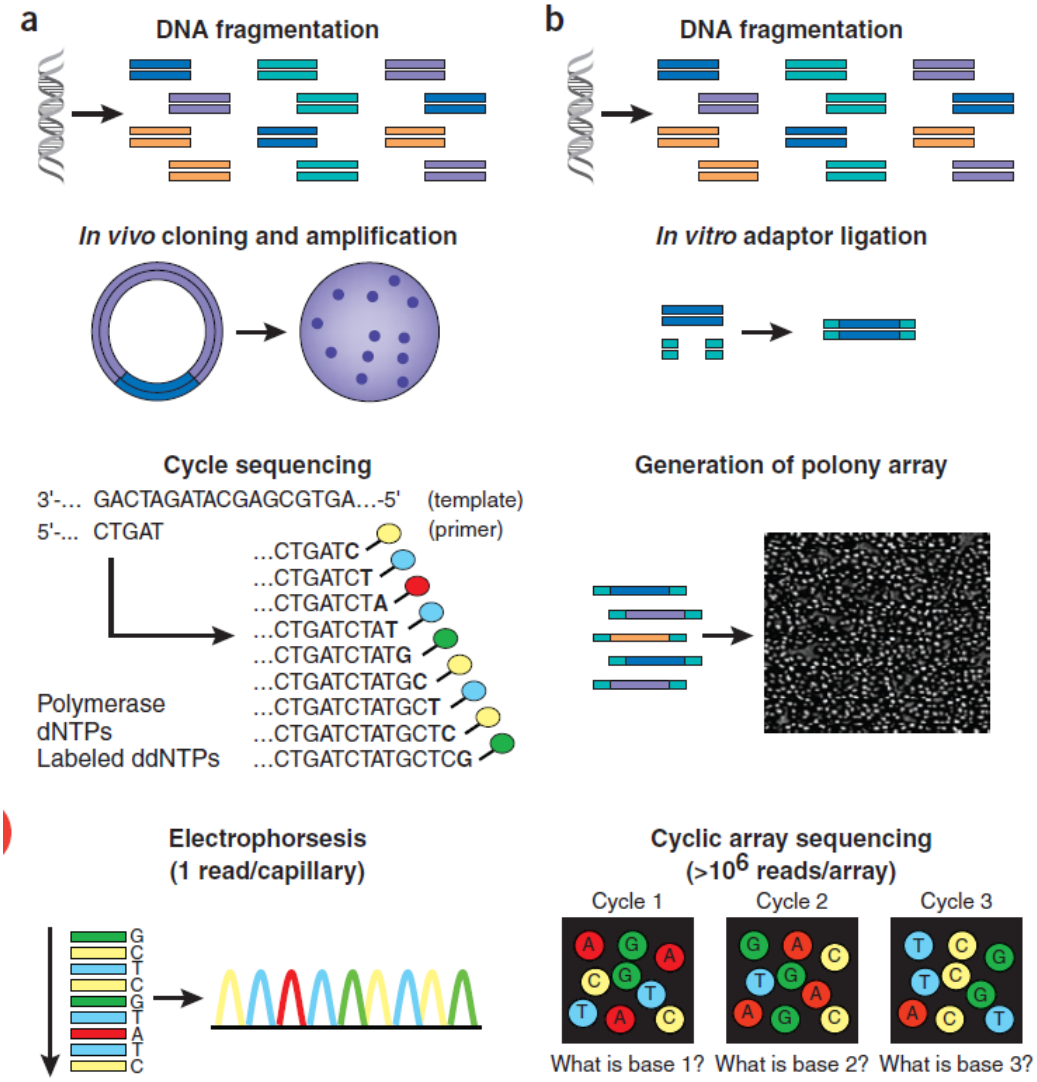



Figure 6: "First versus Next Generation Sequencing", Source: Shendure and Hanlee (2008).

(a) "With high-throughput shotgun Sanger sequencing, DNA is fragmented, cloned to a plasmid vector used to transform E.coli. [...] DNA sequence is read out via capillary electrophoresis."

(b) "In shotgun sequencing with cyclic-array methods, common adaptors are ligated to fragmented genomic DNA. [...] Imaging-based detection of fluorescent labels is used to acquire sequencing data on all features in parallel. Successive iterations of enzymatic interrogation and imaging are used to build up a contiguous sequencing read for each array feature."

In the context of the "Human Genome Project" which started in 1990 (Collins 1999), the first composite human genome was sequenced in 2001. The sequencing process took more than one decade at an immense cost of over 3 billion dollars (Niedringhaus et al. 2011). Today, thanks to improvements in bioinformatics and due to the development of high-throughput sequencing technologies, it is now possible to map a human genome within a few days (The Economist 2011). These high-throughput NGS devices comprise a combination of a synchronized reagent wash of nucleoside triphosphates (NTPs) and a synchronized optical detection method. Furthermore, they

are based on sequencing by ligation or sequencing by synthesis, including methods such as pyro-sequencing and reversible chain termination (Niedringhaus et al. 2011). Sequencing machines, such as Roche 454 FLX, Illumina Solexa Genome Analyzer, Helico/Helioscope, Applied Biosystems SOLiD and Pacific Biosciences SMRT are commonly used (Mardis 2008). These instruments permit efficient sample preparation and comprehend a complex combination of enzymology, chemistry, high-resolution optics (cf. Figure 6b), hardware and analysis software. Each of those technologies tries to amplify single strands of a fragment library, carrying out sequencing reactions on the amplified strands which rests upon the "old" Sanger method (cf. Figure 6b). The fragment libraries are created by annealing platform-specific linkers to the fragments directly obtained from the DNA (or another source). That way, molecules can be selectively amplified by PCR (polymerase chain reaction). Helicos and Pacific Biosystems devices are "single-molecule" sequencers, which implies that they do not need a PCR prior to the sequencing process. Thanks to an improved imaging of sequencing reactions, such as high-definition DNA microarrays, a periodic charge-coupled device snapshot of 96 fixed capillaries, running time can be massively reduced. In this way, Illumina and Applied Biosystems achieve tens of millions of reads each run (Mardis 2008). In whole genome analysis a huge number of genetic variants are investigated using chip analysis.

In order to decrease the costs of sequencing the human genome to less than 1000 USD, the National Human Genome Research Institute (2015) has funded teams to develop alternative methods of DNA sequencing using scanning tunneling electron microscopes (TEM), fluorescence resonance energy transfer (FRET) techniques, single-molecule detection and protein nanopores – known as "Third generation technologies". Two promising methods by Pacific Biosciences and Complete Genomics still use the optical fluorescent detection method, while increasing sequencing speed and throughput. In contrast, Ion Torrent's relies on ion-sensitive field effect transistors (ISFETs) to elude the need of optical detection. Nanopore technologies (cf. Figure 7), as Oxford Nanopore, do not need DNA amplification prior to the sequencing process because the change in the conductivity of a nanopore molecule is supposed to identify nucleotides. Thus, the identification of nucleotides can be carried out directly without any hybridization processes or PCR prior to the DNA analysis. However, this technology is still not applicable due to the small DNA throughput achieved (Niedringhaus et al. 2011).

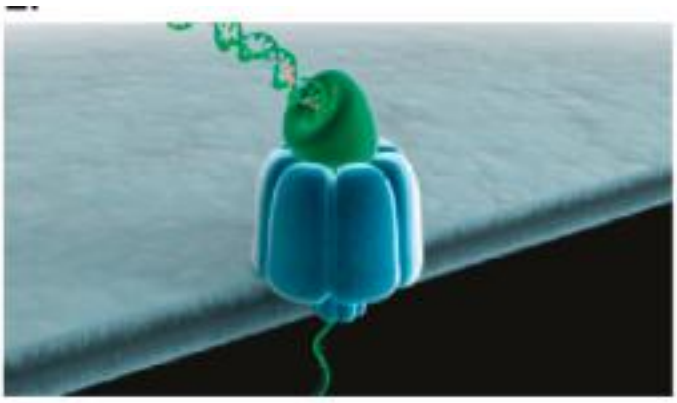


Figure 7: “Nanopore sequencing”, Source: Niedringhaus et al. (2011).
ssDNA is threaded through a protein (nanopore) which reads out individual bases while the strand remains intact.

## 3.3. Bioinformatics tools for genetic tests

New genome sequencing methods are challenged by the limited capacity to process, store, revise, and interpret data. In this regard, bioinformatics tools in the field of genomic research are a strategic discipline, essential for the fast knowledge accumulation in genomic data research.

Thanks to improvements in bioinformatics evaluation methods of genomic data, it has become possible to evaluate genetic DNA information with smaller sample sizes and in a cost-efficient way (Deutscher Ethikrar 2013:32). Meanwhile, there is a wide-range of bioinformatics software libraries available online. Software is an essential tool to analyze high-throughput genetic information at any stage. First of all, software is necessary to locate sequences and make techniques of hybridization possible. Furthermore, software is essential to assemble genomic fragments, a process which needs precise statistical and combinatory algorithms (Deutscher Ethikrat 2013:13).

Bioinformatics software also addresses relevant information on characteristics of genomic data, namely coding sequences, the identification of regulatory sequences, as well as introns and exons, signals for splicing, cellular characteristics and mutations. Also, bioinformatics tools characterize cell biological functions and non-functional protein interactions which are of major importance in the field of genetic research. Likewise, the assembly of bigger DNA sections using “fragmented” primary data relies on bioinformatics methods. Moreover, such methods offer important diagnostic analysis of plausibility control and error detection (Deutscher Ethikrat 2013:38-9).

Importantly, after the primary analysis of “raw” data and data collection and evaluation, bioinformatics tools play an important role in data interpretation – the connection of biological

information. Genomic sequences can be linked to physiological and biochemical processes in an organism.

Another important task of bioinformatics addresses the connection of different biological data using mathematical tools and text analysis. This means that gene sections of a genome can be compared with physiological and biochemical processes of an organism. Furthermore, the comparison between different species is enabled by using bioinformatics tools.
However, it should be mentioned that bioinformatics results follow inductive hypothesises, which implies that evidence of hypothesises can be only given by validating scientific experiments. In fact, it can be challenging to draw conclusions from epidemiological data analysis to evidence particular clinical cases (Deutscher Ethikrat 2013:39).

Finally, bioinformatics software contributes to confidentiality and data privacy due to algorithms that anonymize or decode individual information (which offers the possibility to re-contact data donors) (Deutscher Ethikrat 2013:39).

The described software tools are supposed to be the first step to understand biological systems, by adapting bioinformatics strategies to non-linear connections between different biological levels. "Systems biology" tries to integrate genetic, physiological and biochemical data into a computational modeling system of complex biological systems (Bundesministerium für Bildung und Forschung 2014, Barrett et al. 2008).

It can be argued that the rapid development of new bioinformatics methods has far-reaching consequences for medicine and society that needs ethical reflection. Mass data collection is challenged by data confidentiality issues, especially with regard to "unspecific" data collection of vast WGS/WES studies. Furthermore, there could be a tendency to establish predictive genetic tests, based on genetic data profiles of populations and certain risk groups, as the probability of risk is based on the comparison between individual genetic dispositions and disposition of a whole group (population) (Deutscher Ethikrat 2013:41-2). Since "systems biology" is still a young research field, the described models are expected to progress rapidly in the coming years.

## 3.4. Adequacy of genetic test methods

The reliability and diagnostic and predictive significance of genetic tests are of major importance in research and clinical diagnostics. While research particularly focuses on the technical validity of a

genetic test, its medical application is also challenged by the application of epidemiological facts and statistical risks that are transferred to individual persons (Jones et al. 2002). Moreover, the interpretation of a test - the association of genotype and phenotype - must be evident (Deutscher Ethikrat 2013:33).

### 3.4.1. Technical validity: specificity and sensitivity of genetic tests

The significance of a genetic test strongly depends on the sensitivity of the test applied to a particular case. Thus, the technical validity of a test is constituted by its specificity and sensitivity.
A genetic test is 100% specific if it is positive for individuals carrying a particular characteristic and if it is negative for individuals lacking the specific characteristic. Decreased specificity of a test means that the test result can be positive for non-carriers (false-positive test results).
A genetic test is 100% sensitive if carriers of a characteristic are tested positive. A non-sensitive test runs risk to overlook positive carriers (false-negative test result).
A false-positive diagnosis can be harmful if preventive or therapeutic measures are performed which are not necessary. In contrast, false-negative test results can lead to harm in case of available preventive and therapeutic interventions which are omitted (Deutscher Ethikrat 2013:50-52). False-positive, as well as false-negative results can be caused by errors during the DNA copy process of the test which is essential for the amplification of DNA material. Regarding the practical implementation of a test, the risk of wrong test results is never adjusted to zero (Jones et al. 2002).

Both, specificity and sensitivity can be quantitatively measured. It is possible to calculate the frequency of false-positive and false-negative test results by using the prevalence of a genetic characteristic in the population. Testing rare mutations at many different genetic loci, leads to a high number of false-positive results. Likewise, there are many genetic aberrations which are not detected in monogenetic disorders due to a high number of non-detected rare alleles and allelic heterogeneity (Deutscher Ethikrat 2013:52).

### 3.4.2. Predictive transfer of statistic risks to individuals

The following paragraph addresses findings of genetic tests that are often predictive statements about a future phenotypic characteristic.
Additionally to the described technical uncertainty, predictive tests can fail to predict phenotypic characteristics when transferring epidemiological/statistical risks to an individual. In other words, predictive tests try to associate phenotypic and genotypic characteristics by using data collected

from populations. Thus, tests cannot individually diagnose people because the risk analysis refers to the population risk. The indicated risk cannot surely predict the occurrence of a phenotypic characteristic due to additional factors that are necessary for the occurrence of the characteristic ("penetration"). Hence, even if the genetic test indicates the genotype correctly, an individual diagnosis based on the test result cannot be given with certainty.
In consequence, a prediction of the development of a disease is always linked to a certain probability meaning that the individual does not necessarily develop the phenotypic characteristic, although it might be likely. This can have very harmful consequences, in particular when preventive measures (e.g. mastectomy or ovariectomy of breast cancer patients) are taken. Similarly, it can be argued that a test indicating a low risk for certain diseases may harm individuals, especially if the individual could have undergone preventive measures (e.g. preventive examinations) (Deutscher Ethikrat 2013:57-60).

With regard to multi-factorial disorders, it is even more difficult to interpret complex correlations between genotype and phenotype. During the last decades, huge genetic studies (genome wide association studies "GWAS"), including an extended number of participants, were conducted and aimed for more evidence in this regard (Buchanan et al. 2006). Traits, as disease symptoms, were registered and compared with genome wide individual SNP variants or SNP haplotypes. In genome wide association studies, cumulative DNA patterns ("markers") are investigated (Manolio 2010). At this point, it should be mentioned that the transfer of the population risk investigated via GWAS to a single person is different from the accuracy problem in genetic testing. GWAS is a label of a clinical study whereas WGS/WES is the technique or procedure to collect genetic data. Hence, despite the conduction of accurate WGS/WES tests, the statistical analysis of genetic variants found in the population might not truly represent the population risk: it rather happens that statistical evaluation tends to "over-fit" pheno- genotype associations, as non-causal correlations are often brought into a causal connection. Likewise, it happens that relevant genes and the interaction between genes are not detected, so called "under-fitting". In order to establish a connection of phenotypic and genotypic characteristics, long-term studies need to be conducted (Deutscher Ethikrat 2013:59).

In conclusion, the limitation of disease-genotype associations consists in the transfer of epidemiological risks to a single case. However, despite the limitation of using epidemiologic data (e.g. from GWAS), genome wide scans may be useful in terms of a general screening for genetic variants that influence, for instance, the response to drugs (Manolio 2010).

## 3.5. Databases, data storage and privacy

Following up on the importance of bioinformatics software, databases play a most important role in the interpretation process of genetic data. Internationally cooperating biodatabanks which compile medical information for research and clinical care build the fundamental basis for further progress in genetic data interpretation. However, clinicians face problems, as data of ambulatory patients is more and more outsourced to external institutions, which implies that there is less data available for research at university centers (Deutscher Ethikrat 2013:42).

Regarding increasing data storage in remote databases, the problem of privacy and confidentiality becomes a crucial issue. WGS/WES offers great promise to generate benefits for society. These advances depend on large numbers of individuals who are willing to share their genomic data for research purposes. Moreover, research results are sounder when the connection between genetic variations in whole genome sequence data and specific health and demographic information is part of the research project. Therefore, research and clinical power of WGS/WES data is linked to a large number of data sets including relevant health and disease information (although, admittedly, the use of participant's names and similar personal information is not necessary) (Presidential Commission 2012:22-3).

Genome sequencing determines the complete sequence of DNA in an individual's cells, including all variants within the genome (Presidential Commission 2012:14-9). It can be argued that the amount of information contained in the human genome demands thoughtful data collection and storage, as "sequence data [is] different from other medical information" (Presidential Commission 2012:18).
More specifically, WGS/WES raises concerns about privacy when patients and participants in research projects do not want to give access to their sequenced data and genetic information to other persons. Thus, if these data is accessed without authorization, it can be considered misuse of information. Information revealed in a public space can have negative consequences for an individual, as e.g. the impairment of chances to find a spouse, achieving standing in a community, or pursuing certain careers (Presidential Commission 2012:20).

In conclusion, it can be considered a topic in itself to draw the line between accessible WGS/WES data and data privacy. On the one hand, researchers that are enabled to use vast data resources can advance medical understanding and contribute to the public good. On the other hand, the consequences of widely accessible data, with a special regard to very delicate WGS/WES data, can

possibly harm individuals.

The presidential commission for the study of bioethical issues is addressing crucial questions, as for instance, what information about an individual's genome should be kept private by exploring when, and why genomic information is subject to confidentiality, and information security (Presidential Commission 2012:21).

## 4. Conclusion

The aim of this chapter has been to introduce biological terminology, characteristics and the application range of genetic tests and to give an overview over sequencing technologies, genetic tests and bioinformatics tools, as well as data retention.

So far, it could be pointed out that WGS/WES technologies support significantly discovery and understanding in clinical and basic research as a result of the advances in bioinformatics and sequencing devices. This makes the informed consent in genome data research a crucial topic taking into account the current and future possibilities to use such technologies. Furthermore, this chapter puts emphasis on the fact that genetic tests cannot assure absolute accuracy with respect to sensitivity and specificity. Also, the correlation of genetic aberrations with phenotypic characteristics of an individual has to be handled with care due to complex genotype-phenotype relationships and due to the fact that statistical risks, even if appropriately mirroring the population's risk, cannot be linearly transferred to an individual and its health state.

Hence, with regard to the ethical framework and the development of an informed consent for the feedback of incidental findings, such technical limits should be taken into account. The technical possibilities of WGS/WES research clearly advocate the thoughtful handling of genetic information via an informed consent process.

# Chapter 3. Historical view on informed consent and the return of findings in research

## 1. Introduction

In the following chapter, I will introduce some of the historical references of informed consent in the literature of research ethics. The aim is to present the main ethical hurdles that were identified after the Second World War and the answer to them, in terms of guidelines addressing crucial rights that should be given to research participants. Furthermore, the development of guidelines for informed consent and the return of findings to participants in research influenced law and regulation.

In a first step, the historically most important guidelines that impacted on research practice with humans will be presented. Subsequently, I will present the example of law and regulation guidelines from the U.S., maybe the most common reference for legal frameworks and regulations with regard to research using WGS/WES technologies.

## 2. Historical background on informed consent

Informed consent was originally important in liberal political theory and economic thought which can be dated back to discussions during the European Enlightenment in the 17th and 18th century. The claim of the social contract tradition is to establish a freely given consent legitimating actions of an individual that would be impermissible without consent giving. Basically, informed consent was a measure to counter coercive power and despotism. Thus, the basic idea referred to "volenti non fit iniuria", no injury is done where the subject is willing (Steinbock 2007:1).
The Nuremberg Code was written in 1947, after the Nazi experiments during the Second World War, asserting that all research on human beings requires their voluntary consent prior to the participation in experiments:

> "[…] This means that the person involved should have legal capacity to give consent; should be situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or other ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. […]" (The Nuremberg Code 1949, Article 1).

The first article of the Nuremberg Code uses the term "voluntary consent" instead of "informed

consent", which emphasizes the demand of a freely given consent in the historical light of the Nazi crimes. However, the literature on research ethics considers the Nuremberg code as a paradigmatic reference of "informed consent". Referring to article 1 of the Nuremberg Code, three main characteristics of voluntary consent can be distinguished: the capacity to give consent, non-interference in terms of "free power of choice" and "sufficient knowledge and comprehension".

Apart from the Nazi trials, another exemplary case in history of a clear infraction of research participant's informed consenting can be considered the Syphilis Study conducted in Tuskegee and Alabama during 40 years between 1932 and 1972. The study was promoted by the Federal Public Health Service in the US and acted against an adequate comprehension of the informed consent requirement (Centers of Disease Control and Prevention 2013). Since some participants remained without treatment despite the availability of penicillin, researchers had a control group to investigate the "natural progression of the disease". Although informed consent sheet was signed by the participants – and one major aspect of the informed consent requirement was met – the participation resulted in miscomprehension, as the participants were not informed about the availability of treatment, treatment provision, or the risks of omitted treatment (Johns 2008:86). This means that the missing component of "sufficient knowledge and comprehension" did jeopardize the possibility to give proper informed consent and moreover and the voluntariness of participants which also strongly depends on knowledge and comprehension.

In 1964, the World Medical Association launched the Declaration of Helsinki, which put emphasis on the importance of informed consent. The Declaration of Helsinki is undergoing a continuous revision process and is considered one of the foremost international guidelines for research with human beings (Presidential Commission 2011:97).

Further mile stones in the guideline development were the Belmont Report in 1978 (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research 1978), the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research, which published reports on Protecting Human Subjects (1981) and specifically addressed informed consent. In 1981, the FDA (US Food and Drug Administration) regulation guidelines were revised using the Belmont Report as a template. The Council for International Organizations of Medical Sciences presented in 1983 International Ethical Guidelines for Biomedical Research Involving Human Subjects (revised in 1993 and 2002) (CIOMS and WHO 2002). In 1991, the U.S. Department of Health and Human Services issued the Federal Policy of Human Subjects, the Common Rule, which was adopted by 18 federal agencies. Also, the Tri-

Council policy statement (2014) is considered one of the important documents for the protection of human research individuals (WHO 2015).

The following timeline gives a historical overview of developments in U.S. research ethics and informed consent.

**D. Timeline**[13]

| | |
|---|---|
| 1900 | Written contracts between researchers and participants are used in the Walter Reed Yellow Fever Experiment, an intentional exposure study of the mechanism of yellow fever transmission. This was the first documented instance of use of the informed consent process in a major research study. |
| 1932 | U.S. Public Health Service Syphilis Study in Tuskegee, Alabama begins. |
| 1946-1948 | U.S. Public Health Service sexually transmitted disease studies are conducted in Guatemala (discovered in 2010). |
| 1947 | Nuremberg Code is implemented.[14] |
| 1962 | Kefauver-Harris amendments to the Federal Food, Drug and Cosmetics Act is passed and signed into law in response to the thalidomide tragedy; from this point forward, clinical drug testing requires informed consent.[15] |
| 1964 | *Declaration of Helsinki* is published.[16] |
| 1966 | Henry Beecher's *New England Journal of Medicine* article, "Ethics and Clinical Research," is published, identifying 22 cases of unethical research.[17] |
| 1974 | Congress passes the National Research Act, which establishes the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to consider and provide guidance for ethical human subjects research. |
| 1978 | National Commission publishes the *Belmont Report*.[18] |
| 1980-1983 | President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research publishes reports including *Protecting Human Subjects* (1981), which specifically addresses informed consent. |
| 1981 | FDA regulations are revised in light of the *Belmont Report*. |
| 1982 | Council for International Organizations of Medical Sciences publishes *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (revised in 1993 and 2002).[19] |
| | As of 1982, 30 states have implemented informed consent legislation.[20] |

Table 1: "Historical overview research ethics guidelines" Source: Berg et al. (2001:44)

Contemporary discussions suggest that informed consent should play a more important role in

biomedical issues than in the late 1940s, when the Nuremberg Code was written. For instance, informed consent requirements have been extended to clinical settings (Steinbock 2007:4).

As shown in the Table 1, regulations (suggested by several guidelines) for the use of personal and medical information and human tissues were implemented in clinical and research practice.
Furthermore, the informed consent requirement has been incorporated into the regulations governing data protection, use of human tissues and genetic technologies, and is thus mandatory for the secondary use of information and tissues (Steinbock 2007:4-5).
These examples show that the informed consent guidelines have to be continuously adapted in order to guide informed consent practices with respect to novel and future developments in medicine. For instance, in the Bioethics Commission's report "Privacy and Progress in Whole Genome Sequencing" (Presidential Commission 2012), sequencing of whole genomes is exemplified as technological advance that needs evolving concepts of informed consent. Yet the complexity and the data volume of WGS/WES needs to include more advanced elements for obtaining informed consent, such as the expected risks, benefits, likely outcomes, as well as the emphasis that uncertainty is inherent to sequencing technologies (Grady 2015).

Steinbock (2007:2) points out that informed consent is nowadays so well established in clinical and research practice that its justification is rarely questioned.

In this section, a short historical overview on the informed consent requirement and the development of guidelines has been presented. In the next section, the current situation regarding legal implementations of the informed consent requirement, as well as on the return of incidental findings will be given.

## 3. Law and Regulation Guidelines: the Case of the United States

In the following paragraphs, the scope of informed consent in whole genome research settings, as well as the legal guidance regulating the return of findings will be depicted. The example of the U.S. may be the most demonstrative case for the implementation of sequencing technologies due to its pioneering work in the application of WGS/WES and in guideline and regulation development. Furthermore, most of the English-language literature dealing with the implementation of informed consent and the return of findings focuses on legal frameworks implemented in the United States. The guidelines that are subject to this thesis and serve as references are first and foremost issued by U.S. American institutions (e.g. the Presidential Commission for the Study of Bioethical issues).

Legal guidance regarding genetic non-discrimination, such as the U.S. federal "Genetic Information Nondiscrimination Act" (GINA) addressing the question how to deal with genetic data and data protection of large-scale genomic data (Presidential Commission 2012:52) will not be part of this chapter, as the scope of the dissertation will be on the counseling process between research bodies and research participants and does not focus on confidentiality issues or the impact of data disclosure to third parties.

Federal regulations were codified by the U.S. Department of Health and Human Services in 1991 (HHS 1991) and are legally binding rules for conducted research involving human participants. Eighteen federal agencies have implemented the Common Rule. Additionally, the U.S. Food and Drug Administration (FDA) codified its policy for the protection of human subjects and regulates research trials for products which are in the scope of FDA (Figure 8 "Federal Regulation of Human Subjects in Research", Presidential Commission 2011).

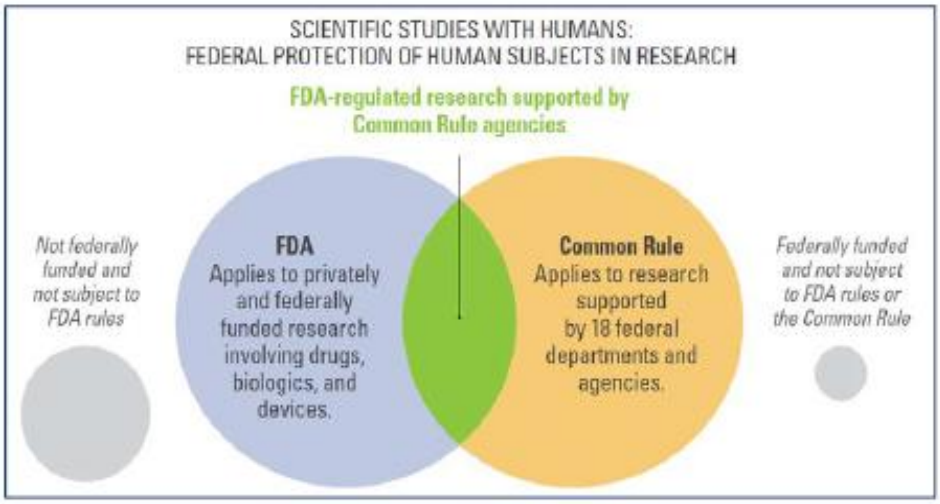



Figure 8: "Federal Regulation of Human Subjects in Research"
Source: Presidential Commission for the Study of Bioethical Issues (2011:31)

The Common Rule applies to research with human subjects and is promoted by the 18 federal departments or agencies. Importance is given to general requirements for informed consent, including an explanation of the research study, the statement of expected benefits and potential risks, an explanation of confidentiality, available medical care and compensation for injuries that can be traced back to the research experiment, and to the statement of voluntariness - withdrawal from the research study at any point of time (Presidential Commission 2011).

All 50 states have adopted some informed consent law, but there are still huge differences regarding legal obligations in clinical and research settings between different states (Presidential Commission 2012:133). For instance, completely different legal obligations are coming into effect, when genetic information is generated and stored as part of the research protocol (Presidential Commission 2011:133).

Regarding the case of the United States, there is no federal law or state law addressing the return of research results to individuals participating in research studies as yet (Wolf 2012). Nonetheless, there are regulations, e.g. the Federal Policy for the Protection of Human Subjects, protecting humans enrolled in research projects. Notably, the regulation document addresses the informed consent process, and in particular, the information disclosure of potential benefits and risks connected with research projects. Moreover, the ICH-GCP (ICH-GCP 1996) harmonization guidelines defined informed consent as "[…] the process by which a person freely confirms their willingness to participate in clinical research after having been informed of all parts of the study that are relevant to the individual's decision to participate".

Potentially beneficial or harmful information are crucial features attributed to research findings (Presidential Commission 2013:81). In the United States, regulations on the revealing of patient-specific results concern results obtained in research laboratories that are certificated as CLIA laboratories, laboratories committed to federal quality standards. The Clinical Laboratory Improvement Amendments of 1988 (CLIA) regulations include federal standards which can be applied to "[…] all U.S. American facilities that test human specimens for health assessment or to diagnose, prevent, or treat disease." (Centers of Medicare and Medicaid Services 2015).

Since only few research laboratories choose to obtain CLIA certification (CLIA certification covers around 251,000 laboratory entities, Centers of Medicare and Medicaid Services 2015), it is currently under discussion whether those laboratories without CLIA certificate should return findings to research participants (Presidential Commission 2013). It was furthermore argued that findings generated in non-CLIA institutions should be revealed as long as they are indicated as research findings and not as clinical findings (Fabsitz et al. 2010). However, this can be considered rather a particular problem connected to the U.S. regulations than an ethical concern.

In 1999, the National Bioethics Advisory Commission (NBAC) favored the model not to return incidental research findings, except in rare circumstances. Over time, several organizations and advisory commission complemented guidelines, suggesting that patients and participants should be

offered to learn about intended and incidental findings which can affect their health (Wolf et al. 2012, Bradbury, McCormick and Robson 2014). The American College of Medical Genetics and Genomics (ACMG) (2013)[1] developed recommendations for the report of incidental findings in the context of WGS/WES. The ACMG emphasizes the importance of disclosing the possibility of such incidental findings prior to WGS/WES, as well as the importance of reporting incidental results which are outlined in the recommendations to individuals in a clinical context (Green et al. 2013). The Presidential Commission (2013) also released guiding principles specifically considering return of findings in WGS/WES research. Importantly, those recommendations give weight to the anticipation of the potential of incidental findings, the communication of this potential and a plan for the disclosure of findings to research participants. Moreover, topics like the share of decision making or the right to reject receipt of incidental findings are addressed (Presidential Commission 2013).

Considering minors, there can be additional questions raised with regard to the legal feasibility of returning future WGS/WES finding. Federal law sets the required age for consent at age 18, while state laws allow consent by minors who are older than 14 years (The Family Educational Rights and Privacy Act, 20 U.S.C. §1232g; 34 C.F.R. §99). For instance, the Presidential Commission (2012:148) reproaches the federal and state laws for not regulating the return of future findings in case of minors. Generally it is concluded, that most genetic aberrations should not be predicatively tested in minors. Nonetheless, WGS/WES comprises genetic analysis of all genes. Thus, it is unclear if researchers should feel compelled to re-contact these children as adults, in particular if there is evidence on other genetic aberrations at future points of time (Presidential Commission 2012:148-9).

The American College of Medical Genetics and Genomics (ACMG) (2013) states that seeking for genetic aberrations could be medically important to a child's future or the family even if such findings are linked to an adult-onset of disease. The ethical concerns about providing the clinicians of children with genetic risk information are outweighed by the potential benefits to the future health of the child and the child's parents (Green et al. 2013).

## 4. Conclusion

The presentation of attempts in the course of history to improve informed consent requirements and

[1] There has been an update in 2014 by the ACMG emphasizing that there is a consensus among ACMG members that patients should have an opportunity to opt out of the analysis of medically actionable genes when undergoing whole exome or genome sequencing (ACMG 2014: "ACMG Updates Recommendation on "Opt Out" for Genome Sequencing Return of Results").

how informed consent is brought into current legal practice has been the main objective of this chapter. Especially the historical review on informed consent shows that informed consent has been always adapted to new research fields or responded to historical events which clearly infracted research individuals' rights. Applied to the case of WGS/WES, it can be put on record that the development of informed consent has not yet come to an end. This means that new technologies, such as WGS/WES, demand a continuous adaption of the informed consent requirement. Also, since the implementation of WGS/WES procedures in clinical research is accelerated due the huge cost reduction potential of sequencing technologies, an informed consent model tailored to WGS/WES would substantially contribute to a further adaption of informed consent to these external conditions.

Regarding the aspect of informed consent in the feedback process of incidental findings, it is of utmost importance to point out, that homogenous legal frameworks are still missing (example in the United States). This uncertainty demonstrates that there is an urgent need to clarify recommendations on the return on findings and that ethical frameworks are needed to guide the return of research results. With regard to Chapter 4, there will be a major paragraph carving out what kind of findings should be necessarily reported to research individuals.

# Chapter 4. Ethical framework of informed consent models in WGS/WES and the disclosure of genomic data research findings

## 1. Introduction

The objective of this chapter is to introduce a new consent model that I call the "iterative feedback model" for whole genomic data collection and disclosure of incidental findings in human health research studies. The model approaches the ethical demands to informed consent models in the specific setting of research studies using WGS/WES procedures by adapting to specific problems and characteristics arising in the context of WGS/WES data and the disclosure of incidental findings.

In order to introduce the model, I will first establish and justify the practical scope of the present dissertation. Secondly, I will reconstruct already existing informed consent models for research using WGS/WES procedures. In the next step, those models will be evaluated by challenging them with ethical principles that are considered crucial in research ethics (cf. Appelbaum et al. 2014). Finally, the "iterative feedback model" will be developed and evaluated on the basis of the ethical framework while focusing on the disclosure of incidental findings to research subjects.

## 2. Case study

The objective of the following case study is to present a practical and intuitive application of WGS/WES in a research setting. The analysis of a real case is supposed to facilitate the understanding of ethical issues and its further discussion when considering the informed consent process for the disclosure of incidental findings in research studies using WGS/WES procedures.

More specifically, the example chosen for analysis is a case of GWAS (genome wide association studies) which have been introduced in chapter two (cf. "Predictive transfer of statistical risks to individuals"). GWAS is a subtype of human health research using WGS/WES procedures. In the broad application range of WGS/WES procedures, GWAS specifically examine a big number of genetic variants in different individuals and associate them with phenotypic traits (Buchnan et al. 2006) like e.g. rare diseases. GWAS demonstrate the case of incidental findings that likely appear when searching for genome wide associations with traits due to the investigation of many genes and of many participants. Therefore, the further ethical analysis of research studies using WGS/WES procedures is in particular tailored to the ethical problems arising in the course of a particular GWAS of rare diseases.

**Case: The rare diseases genomes project (NHS-UK)**

In 2013, the "Rare Diseases Genomes Project" was announced in the United Kingdom, a collaborative project between the University of Cambridge, Illumina Inc. and Genomics England Ltd. It is a project that aims to sequence 10,000 genomes of rare disease patients within three years and is conducted together with England's "100k Genome Project" (www.genomicsengland.co.uk) (Perdeaux 2013). Patients with rare diseases and conditions that were likely to have a genetic basis could participate in the project. Scientists hope that the projects "[…] will bring enormous improvements to the care of patients with rare diseases […]" (Bradley 2014).

Usually, patients suffering from rare diseases face a long time until they obtain a diagnosis. For instance, two siblings with an unusual muscle wasting disease had to wait for 20 years until they were diagnosed at a cost of of more than 14,000 pounds. Whole exome sequencing which cost approximately 1000 pounds revealed that heterozygous mutations in the SACS (www.omim.org/entry/604490) gene were likely to be disease causing (Perdeaux 2013).

Furthermore, researchers participating in the project are allowed to access the data and use them as de-indentified information for epidemiological and drug discovery studies or to identify patients for clinical trials. The NHS (National Health Service) assured the security of the collected data (Perdeaux 2013).

This case brings into play several interesting issues to consider. First of all, the example shows that using WGS/WES procedures in research studies can be an adequate and common method to investigate new genes that could be of importance for the pathogenesis of disease, not least due to the improving sequencing technology allowing fast and cheap data collection (Niedringhaus et al. 2011). Notwithstanding, there are currently no statutes directly regulating the return of research findings to research participants (Presidential Commission 2013).

However, whole genome sequencing produces a vast amount of data of research individuals which can have huge implications for the life of these individuals. For instance, it is very likely to find a great number of variants of unknown significance, complicating the interpretation of results. Furthermore, "incidental findings" could reveal that a research participant is at risk of developing a disease which is unrelated to the former physiological abnormalities. In this regard, the question might be, whether to return incidental findings or not. Since the return of information may have

implications for the participant's decisions, as e.g. reproduction, advocates of the principle of "personal utility" (cf. "theoretical framework") might favour the full disclosure of relevant information if the participant agrees. Moreover, it is frequently argued that supporters of concepts as personal entrustment or reciprocity demand the disclosure of all relevant information as part of the researcher's obligations (Secretary's Advisory Committee on Genetic Testing 2000). For this reason, some have argued that researchers ought to disclose all findings independently of the clinical implications they may have (Whitney and McCullough 2007).

In contrast, it can be criticized that incidental findings without "analytical" and/or "clinical validity" and/or "clinical utility" do not contribute to a meaningful information return, as the data does not reveal significant findings that could have consequences for the participant. Other authors suggested that findings should at least exhibit reproductive significance (the extent to which a finding has medical implications for one's self offspring) or the seriousness of potential harm (Claufield et al. 2008).
Additionally, such data is prone to misinterpretation by participants who are probably not familiar with the distinction between analytical validity, clinical validity and clinical utility. Another issue related to the question of confidentiality, is the disclosure of findings, once they arise, to other family members who could be affected by the same genetic aberrations. This might be a serious problem especially in the case of rare diseases, as individuals with the same syndrome are often related.

## 3. Scope of the thesis

In this section, I will state the scope of the main thesis in order to develop the iterative informed consent model.

> *Scope of the iterative inform consent model.* In this work I will focus on the informed consent process of potential individual research participants in human health research study using whole genomic sequencing (WGS)/whole exome sequencing (WES) procedures, as well as on the disclosure of incidental findings after a study is conducted.

An **Informed consent model** is the application of informed consent theory in practice. Informed consent models incorporate general principles and the groundwork of informed consent theories by interpreting them and applying them to a particular question or problem. In this dissertation, the particular problem addresses how incidental findings, if any, should be revealed to individual

research participants in studies using WGS/WES procedures. Ideally, an informed consent model would be a consistent and useful application in practice of the informed consent requirement (Merritt 2011).

Referring to **research studies with human subjects using WGS/WES procedures,** I will focus on the informed consent process in research projects involving participants who are already patients in a medical context, excluding healthy persons. The term **WGS/WES procedures** refers to technical methods that are used to inquire conditions, as diseases.

The data release of WGS/WES research studies can be subdivided in several categories. As primary objective, human health research studies aim for a public release of data via publications. Generally, genomic data can deal with general study results, or with individual study results, comprising incidental findings not primary sought for in research studies involving human research subjects (Secretary's Advisory Committee on Human Research Protections 2000). The definition of incidental findings, respectively the heterogeneity of definitions found in the literature will be discussed below.

Furthermore, research studies are not primarily conducted to obtain significant results for clinical testing, as research results do not always comprise clinically valid data like clinical tests. However, even if research results cannot provide the accuracy of clinical testing, there might be important findings to report (that could be validated in further clinical studies). As an alternative to the recommendations by the National Bioethics Advisory Commission (NBAC) (1999), in which the disclosure of incidental findings is only recommended in case of significant implications for the participant's health and in case of an action available to treat the associated disease, I will develop a novel framework for the disclosure of incidental findings (cf. "General argument: constructing the iterative feedback informed consent model").

### 3.1 Ethical problems outside the scope of the current presentation of the iterative informed consent model

There are many ethical problems arising in WGS/WES research studies with human subjects that are not focus of the thesis, but valuable for further ethical analysis and discussion. Particularly important ethical problems closely connected with the topic of the thesis will be mentioned in the following text, but will not be addressed due to the limited space of the thesis. However, I believe it is important to state these problems explicitly to complement the positive definition of the scope of

the thesis in the previous section. Also, they might be interesting paths to follow in future research and extensions of the iterative informed consent model.

*Obligations towards third parties*. Researchers' obligations towards third parties are not addressed in this dissertation. For instance, third parties, as family members, could be involved in the WGS/WES disclosure process of findings due to their close degree of relationship to the research participant. Even though the thesis does not address these ethical issues, I will adopt the principle "not to harm third parties" which implies that in case of conflicts of interests between research individuals and other parties, the integrity of other individuals will be prioritized.

*Confidentiality*. Likewise, I will not focus on confidentiality issues towards the individual research participants. Thus, the ethical revision of further data use in epidemiological and drug studies, as well as in data retention, will not be discussed. As a side note, it can be mentioned that data protection and dealing with collected large-scale genomic data and its privacy concerns is one big issue raised in the scope of the Human Genome Project launched in 1990. One important task addresses the question how to safely store genetic information that has grown exponentially (Presidential Commission 2012:52). Confidentiality is of utmost importance to protect participants' data that should be restrictedly accessible to third parties.

*Storing, sharing and distributing genomic information*. Lastly, storing and distributing genomic data is not within the scope of this thesis. An example linked to data retention and the research making use of already stored data is biobank research that is usually linked to practical considerations distinct from other research settings. Biobank research will be also excluded from the focus of this thesis. One major problem that we face in the context of biobanking is the de-identification of stored data that cannot be connected to particular individuals, which makes re-identification difficult (Presidential Commission 2013:80).

# 4. Reconstruction of the theoretical framework for the ethical discussion on incidental findings

## 4.1 Whole genome data

In order to design a consent model for the disclosure of incidental findings in human health research using WGS/WES procedures, the advantages and disadvantage of several consent models as well as crucial ethical principles should be taken into account. However, prior to this analysis it is necessary

to characterize whole genome data. This approach shall furthermore build the basis for the development of an ethical analysis tailored to the characteristics of data collected during the conduct of research studies using WGS/WES procedures. Generally spoken, characteristics of WGS/WES data are crucial for the evaluation of an informed consent model for the disclosure of incidental findings in research studies using WGS/WES procedures, in order to advocate a more specific, broad, autonomous, etc. informed consent, as it will be discussed in the course of chapter four. *Box 1* shows the characteristics of WGS/WES data I considered important for the evaluation of informed consent models. In the following paragraph, those characteristics will be explained in more detail.

One important characteristic of WGS/WES data for the evaluation of an informed consent model is the **predictability of health outcome**. Predictable health outcomes usually attribute a probability to a future health state whereas inevitable health outcome are certain events. As explained in chapter two, predicting health outcomes is always based on a statistical risk that is transferred to an individual case. In this way, whole genome data can eventually be linked to future health events of the research participant and his family members. However, the probability linked to a health outcome indicates a chance for the individual to develop a disease. Even if a research finding does not cause physical harm to the participant immediately after testing, the knowledge about the finding can lead to psychological harm, emotional or cognitive disturbances such as worry, fear, depression or anxiety (Institutional Review Board for Social and Behavioral Sciences University of Virginia 2015), due to possible future health impairments. Thus, when designing an informed consent model, it should be taken into consideration that predictable health states can be a source of psychological harm. Furthermore, therapeutic and preventive measures could have severe physical consequences for participants (e.g. a mastectomy and oophorectomy in case of an elevated risk for breast and ovarian cancer). Therefore, an informed consent model should explain the alternatives of therapeutic and preventive measures and the inherent risks corresponding to the alternatives an individual has.

Moreover, collected data include a set of very **heterogeneous information** that can refer to a variety of psychological or physical predispositions. For instance, such findings can be associated with mental disorders like Alzheimer's disease or Huntington's disease. Some gene aberrations found in WGS/WES data sets can only be applied to one sex of the immediate family tree (as BRCA1/2 is more severe in females). Furthermore, the risk to develop a certain disorder varies among diseases and their correlated genetic aberrations. Gene mutations show different risks for the development of a certain disease.

Another characteristic of WGS/WES data for the evaluation of informed consent models is **irreversibility** of genetic information. Once, genetic information is disclosed, there is no reclaiming it, as an individual's genetic information does not change over time (Genomics law report 2009). This applies to germ line mutations that are present in all somatic cells during the whole life of an individual. In contrast to somatic mutations that are found only in certain cell types (e.g. cancer cells) and which can change their genetic disposition, germ line mutations are enduring entities. Regarding the example of the GWAS of the rare diseases genomes project, it is in particular focused on a search for germ line mutations causing certain health conditions. Research on this type of mutation implies that at the point of time when information is revealed, unchangeable facts are disclosed which potentially change a person's life-style, expectations, planning etc. Thus, genetic information could be the basis for discrimination for an individual`s whole life.

**Interpretation and knowledge** about genetic data change over time. For instance, variants of unknown significance can "turn into" scientifically confirmed mutations or variants with or without pathogenic effects after the introduction of new research results. "Genetic information" is based on genetic loci which are statistically correlated with phenotypic events (as diseases). Without the correlation between phenotype and genotype, genetic analysis cannot be used in terms of a medical exam (cf. Chapter two, 2.4 "Diagnostic, prognostic and predictive genetic analysis"). Anticipating the demands towards an informed consent model, changing interpretation and knowledge about genetic data can justify a repetitive (iterative) genetic counselling process.

**Uncertainty** is a crucial characteristic that should be taken into consideration when dealing with WGS/WES data. There are unclear phenotype-genotype correlations (variants of unknown significance). In many cases, a correlation may not be fully understood (variants of unclear significance) or remains unknown at the time of study.

The term **privacy** applies to WGS/WES data and the evaluation of informed consent models. Genomic data is private and delicate data. The term "private data" is linked to personal and intimate data which demands thoughtful consideration and analysis (cf. theoretical framework).

Finally, with regard to the evaluation of informed consent models, it is important to consider the **connectedness of information** as well as the **reach** of genetic data. Genetic mutations also concern relatives and off-spring and are of importance for family planning.

**Box 1**

**1. Characteristics of WGS/WES data**

**1.1. Characteristics of WGS/WES information and interpretation**

- Heterogeneity. Heterogeneous information (information concerning mental, physical dispositions, disorders, minor risks etc.)
- Irreversibility. Information does not change over time. Genetic information is contained in the genetic code linking genotypic and phenotypic characteristics (gen-protein relationship).
- Interpretation. Interpretation (propositional knowledge) of genetic information is based on the correlation of genetic loci and the occurrence of events affecting an organism/individual.
- Connectedness. The disclosure of genetic information affects not only individuals but relatives and off-spring.
- Uncertainty. There are unclear phenotype-genotype correlations (variants of unknown significance)

**1.2. Consequences for return of results (ROR)**

- Predictability. The probability to develop a certain disease, disorder or another physical event can be indicated.
- Reach. Genetic information can involve family members and off-spring.
- Privacy. The term "private data" is linked to personal and intimate data. Genetic data is private data.

**WGS/WES data** is a raw, but already purified (from inaccurate sequencing results) data set of the base pairs constituting our genome, respectively exome. Data is obtained by sequencing DNA fragments. Those sequenced base pairs are eventually reassembled in the data set.

**WGS/WES information (the genetic code)** refers to genes which have the informational property that they code for amino acid sequences of protein molecules via transcription and translation processes (Godfrey-Smith and Sterelny 2007). The protein molecules interact in the organism,

constituting the phenotype of a being. Thus, the information of genetic data is contained in the code.

**Knowledge about genetic information** is propositional knowledge of facts about the statistical correlation of changes in base pairs and events affecting the whole organism via protein modification. Together with the knowledge about pathway interactions between protein molecules, physiological processes can be partially reconstructed and eventually linked to diseases.

## 4.2 Key concepts for discussing the disclosure of incidental findings in genomic research

The discussion about the return of genomic data and the disclosure of incidental findings has generated a particular vocabulary that it is necessary to introduce in order to avoid confusion when discussing the advantages and disadvantages of several informed consent models, included the "iterative feedback model" presented here. As Eckstein et al. (2014) state, lack of clarity about key terms can sometimes lead to the contrary recommendations for the return of findings. Hence, it is of great importance to define these terms.

I will begin with a first general and usual distinction in practical philosophy between "**concepts"** and "**conceptions**". A "concept" refers to the general structure of A, while various "conceptions" of A are more particular, and even more contested interpretations of the general concept. Thus, concepts are more formal representations of A, while conceptions refer to its substantive formulations (Rawls 1999:19). The concepts that will be presented below, e.g. the concept of "actionability" (in the sense of applicability, practicality) can be interpreted in different ways. For instance, the range of conceptions of "actionability" can reach from "making life-planning decisions more concrete" to "availability of specific treatment". The distinction between concepts and conceptions is important in ethics because many practical problems occur if different conceptions of the same concept are not appropriately applied to or used in a certain context.

**"Analytic validity"** of genetic tests indicates how accurate and reliable the test measures a certain genotype of interest (Secretary's Advisory Committee on Genetic Testing 2000).

The term **"clinical validity"** of genetic tests refers to the accuracy to predict a clinical outcome (Eckstein et al. 2014). Likewise, the NHLBI Working Group defines **"clinical performance"** equivalently to clinical validity of a genetic test as "including its clinical sensitivity and specificity (as related to disease), and positive and negative predictive values" (Richardson 2008, cf. Chapter two "Adequacy of genetic test methods"). However, this definition is challenged by the fact that

genomes show heterogeneity of phenotypes, of gene penetrance, as well as biases in the study populations. Thus, functional relationships between genotype and phenotype remain sometimes unclear (Wolf et al. 2008). For instance, regarding rare diseases, there can be several genes that come into consideration when searching for a disease causing mutations. Also, regarding the small number of participants that can be investigated (due to the rareness of a disease), it can be difficult to generalize phenotype-genotype correlations.

**"Clinical utility"** is linked to the risks and benefits resulting from test use (Burke 2009). Burke (2009) defines clinical utility furthermore as a proven therapeutic or preventive intervention that has the potential to improve a health state connected to the genetic disposition. In contrast, the NHLBI Working Group (2006) refers rather to the likelihood that a performed test will lead to an improved health outcome, which offers a more moderate conception of clinical utility. Thus, this conception of clinical utility takes future beneficial treatments into consideration that are not yet available today. To tie up to the example of the rare diseases, the outcome of a genetic test should potentially improve the future health state of an individual, e.g. via a (future) more target-specific treatment.
Likewise, the term "clinical relevance" is closely linked to clinical utility, but emphasizes the requirement of a clinician's knowledge about an individual's history, family, and environment (Kohane and Taylor 2010).

The concept of **"general/personal utility"** of a genetic test can differ from clinical utility. It might be beneficial for research participants to know about results, even if they remain unrelated to clinical benefits (Secretary's Advisory Committee on Genetic Testing 2000). Thus, even if some research results lack clinical utility because there are no available medical interventions, reporting such findings might be considered important, because it is of interest for the person's own sake (Shkedi-Rafid 2014). This more participant/patient-centered approach acknowledges that actions beyond disease prevention, monitoring and treatment can have meaning for research participants/patients (Gordon 2009).

**"Actionability"** of research findings can be understood in different ways (Eckstein et al. 2014). First of all, actionability of research findings can be interpreted in a **broad sense** of making possible life-plan decisions with regard to particular genetic information. For instance, revealing a research participant that he or she carries a mutation in the Huntington's gene can make life-planning decisions more actionable with regard to reproduction, settling family affairs, etc. Likewise, actionability can be understood as the potential for an improved health outcome including other actions that might change the course of disease (Fabsitz et al. 2010). Coming back to the example,

support by family members or by psychologists could at least improve the psychological harm that is part of the course of disease.

Secondly, in a **narrow sense**, "actionability" refers to "medical actionability" (Green et al. 2013) like the availability of effective medical treatment or prevention. In the case of Huntington's disease, effective treatment to fight the disease and prevention is currently not available. Hence, mutations in the Huntington's gene are not medically actionable at this point in time, but can be actionable in a broad sense.

With respect to an individual's preference whether to know about a research finding or not, the term **"volition"** comes into play. A common formulation is "the expressed preferences of research subjects" (Rothstein 2006).

## 4.3 Informed consent in research using WGS/WES

### *4.3.1 The general definition of informed consent*

The primary aim of this work is to develop an informed consent model for the disclosure of incidental findings in human health research using WGS/WES procedures. In this regard, I ought to define what I understand by informed consent. The understanding of informed consent will be based on the general definition given by Eyal (2011):

> *"Informed consent is shorthand for informed, voluntary and decisionally-capacitated consent.* Consent is considered fully informed when a capacitated (or competent) patient or research subject to whom full disclosures have been made and who understands fully all that has been disclosed, voluntarily consents to treatment or participation on this basis. […] In its most important role in bioethics, informed consent is a legitimacy requirement for certain actions. Inadequately informed consent makes certain intrusions impermissible. […] Roughly, when a sufficiently capacitated adult does not give sufficiently informed and voluntary consent to intervention in her body or her private sphere, then, at least when the intervention is substantial, not trivial, and absent severe jeopardy for third parties, the intervention is impermissible—even when it seeks to assist her, physicians recommend it, third parties would benefit from it, and the patient herself had repeatedly consented to it before expressing a change of mind." (Eyal 2011, emphasis added).

According to this approach, informed consent pursues three aims: (1) full transmission of relevant information, (2) full comprehension as well as (3) voluntariness of subjects that consent.

Importantly, by "full transmission of relevant information" I understand the insurance that the individual receives all *relevant* information to make an informed choice. As stated in the Nuremberg Code (1949, Article 1), research subjects should have "[…] sufficient knowledge […] of the elements of the subject matter involved as to enable him to make an understanding and enlightened choice." For instance, relevant information can be understood as explanation of all health impairments that could be revealed by WGS/WES and that would be important to the research individual. "Full comprehension" means that individuals understand the relevant information, so as to be able to act autonomously (autonomy will explained in more detail in section "ethical principles in the discussion of informed consent models for the return of findings") based on the comprehension of the given information. It should be mentioned that the transmission of relevant information is different from comprehension which has to be considered in the context of the individuals' culture, education etc. (Amaechi Agu et al. 2014). Moreover, the transmission of "complete/full" information from the researcher's point of view could overload the research subject's capacity of decision making. Thus, information revealing has to be adapted to cultural and educational background and the relevance of information evaluated in the light of these external factors. Amaechi Agu et al. (2014) argue after having conducted a survey in Nigeria on the understanding of information when informed consent is taken, that the majority of interviewed individuals desire to be involved in decision-making about their health state even though their understanding is often limited. Hence, they argue that there is a need to simplify information that is often too extensive. Finally, voluntariness of participation refers to a free and uncoerced act of decision-making without fraud. Potential barriers of voluntariness can be (1) "coercion", (2) "undue inducement" or (3) "no choice" situations (Eyal 2011). (1) "Coercion" is defined as "[…] threat to make someone seriously worse off than she is or should be, unless she consents." (2) "Undue inducement" is a term usually meaning that something is being offered that is alluring to an individual which leads to an irrational choice (e.g. cash in hand if the individual undergoes a certain treatment). Lastly, (3) "no choice" options refer to the lack of decent alternatives for an individual (Eyal 2011).

Eyal's already comprehensive definition of informed consent can be compared with other important literature specifically addressing informed consent. This approach aims to complement the definition and puts it into the context of important previous definitions on informed consent for research. However, it will be shown that other references will get back to the three essential elements stated by Eyal (2011): (1) full disclosure of relevant information (2) full comprehension and (3) voluntariness.

Faden and Beauchamp (1986) consider informed consent as "autonomous authorization" comprising a complete and adequate information background, full intentionality and the absence of controlling. These requirements are directly comparable to (1) full transmission of relevant information and (2) comprehension, as the information background is based upon the full disclosure of relevant information and its understanding, as well as (3) voluntariness which is the absence of controlling and a free act. From another perspective, informed consent is one application of the principle "respect for persons" in the Belmont Report, (National Commission 1979) a founding document of research ethics. The principle of "respect for persons" demands, similarly to the definition by Eyal (2011), that "[…] subjects enter into the research voluntarily […]" and "[…] with adequate information" (National Commission 1979), which supports the concepts of information transmission and comprehension of the given information.

### *4.3.2 The fundamental ethical principle behind informed consent: respect of persons or autonomy*

Apart from the three crucial components in the informed consent requirement, "respect towards persons" is an ethical principle (cf. "Ethical principles in the discussion of informed consent models for the return of findings") and another important component closely connected to the fundaments of informed consent. As previously mentioned, informed consent can be regarded as one application of this principle stated in the Belmont Report (National Commission 1979).

The standard way in the literature of research ethics is to interpret the principle of "respect towards persons" as the principle of autonomy. In the Belmont Report it is stated that respect towards persons refers to "[…] the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy." (National Commission 1979)

Hence, if this interpretation is valid, persons should be treated as autonomous agents as far as they are individuals "[…] capable of deliberation about personal goals and of acting under the direction of such deliberation" (National Commission 1979). Those individuals have the "decisional capacity" defined as "ability to perform a task" (Beauchamp & Childress 2009:70) to make their own health care decisions (Charland 2011). Lacking informed consent would imply a lack of respect for persons and hence, deny the individual's freedom to act on its own considered judgments.

Information is mandatory to give the possibility to individuals of making considered judgments (National Commission 1979). Of course, there are cases in which informed consent is not requisite,

such as in research of emergency situations when urgency prevents obtaining informed consent, or in research with identifiable human material and data which does not pose physical risks (Emanuel 2013). Nevertheless, these exceptions cannot be applied to the case of research using WGS/WES procedures, since genetic testing in research is not a "trivial" intervention, linked to substantial risk and not performed in the context of an emergency situation. This means that informed consent is required for research using WGS/WES procedures. Respectively, genetic testing in research is impermissible whenever informed consent is not given.

Furthermore, third parties should not be harmed by an intervention. Interventions remain impermissible without informed consent even if third partied could benefit from interventions. Apart from third parties, even benefits for the individual do not justify an intervention without informed consent. Also, a former consent is invalid as soon as an individual changes his/her mind about a certain health care intervention. In consequence, the principles of autonomy, beneficence and non-maleficence by Beauchamp and Childress (2009) have to be respected for individuals and for third parties.

### *4.3.3 Informed consent for research subjects with lack or impairment of decision-making capacity*

With respect to the rare diseases genomes project, there could be children or disabled persons tested. In order to address the case for research subjects without fully developed decision-making capacity (due to age or mental impairments), Eyal (2011) introduces the possibility of a proxy that acts on behalf of the research individual. "When the antecedent is inapplicable, for instance, when the patient lacks decision-making capacity, similarly spirited rules apply, such as rules delegating consent "authority" to the patient's advance directive or proxy." (Eyal 2011)
Equally to Eyal's definition (2011), the protection of those individuals with diminished autonomy is demanded, referring to the principle of "respect for persons" (National Commission 1979).

### *4.3.4 Informed consent process*

To understand the informed consent requirement, it is important to analyze the idea of the **informed consent process**, a practical consequence of the informed consent theory. The informed consent process is an information exchange including subject recruitment materials, verbal instructions, written materials, question and answer sessions and signature documenting consent with date. Importantly, the term should not be mistaken as a subject's signature on the consent form which is

only part of process (U.S. Food and Drug Administration (FDA) 2015). The informed consent process gives to subjects the opportunity to choose involvement based on information, comprehension and voluntariness (McGuire Dunn and Chadwick 2012; NBAC 2001). The aim is to assure an individual's autonomy, meaning that it has not been deceived or coerced (O'Neill 2003). The ideal informed consent process is an ongoing process which is not completed prior to the end of the study (Chin and Lee 2008).

The informed consent process involves the consent taker reviewing the consent form and all information relevant for the study with the participant and assuring the participant's comprehension of the content. The consent taker is supposed to relate all of the important elements of the study, including the written information by the research ethics committee (REC) (Chin and Lee 2008). If information is not appropriately understood, individuals should not be enrolled in the study, even if they are willing to consent. Otherwise the consent is not truly informed. Thus, time and the opportunity to ask questions must be always given to the individual, as well as all questions concerning the study have to be answered to the participant's satisfaction. Furthermore, the CIOMS guidelines (CIOMS and WHO 2002) prohibit taking informed consent in a language distinct of the participant's language. However, if a witness who does understand the participant's language is present, consent taking can be permitted.
The informed consent form and patient information sheet ("consent form") has to be signed before the participant takes part in the study, meaning that any procedure related to the study has to be performed after the consent. A copy of the consent form must be handed in to the participant.

As part of the informed consent process, there might be occasions where re-consenting is required, although the participant already went through the initial interview of informed consent. This is the case for instance, if significant changes in the protocol occur which might impact on the participant's willingness to participate in the study and if the risk-benefit profile of the study changes due to the data analysis of interim information. A participant is free to refuse and discontinue a study at any point in time even if the consent form has been signed prior to re-consenting at any changes (Chin and Lee 2008).

### 4.4 Additional definitions

In order to avoid confusion, the following definitions are given concerning terms and concepts that are used for the development of an informed consent model in research using WGS/WES technologies.

**Information costs** are part of transaction costs that occur in transactions. Costs concern information processes, as coming to an agreement with the other party, drawing up a contract etc. (Brigham Young University, IS theory 2014). Information costs appear due to the fact that full information provision is not available and that information is usually asymmetrically distributed. Costs have to be spent in order to reach a common information level (Akbari 2014). Applied to WGS/WES data research and the further introduction of the iterative informed consent model, information transmission between researchers, counsellors and participants are inevitably linked to costs due to the information flow.

P**rivacy** can be considered a guarantee to defend human dignity and integrity (Boustein 1964) enhancing personal expression and choice (Schoeman 1992). Privacy is also crucial for intimacy of an individual (Gerstin 1978, Inness 1992). According to Bloustein, "inviolate personality" is a social value (cf. definition of value) that is protected by privacy. Privacy is the basis for the development of meaningful interpersonal relationships (Fried, 1970) and gives individuals the possibility to control the access others have to them (Moore 2003).

The term **"value"** will be used in the traditional sense of intrinsic values "lying at the heart of ethics" (Zimmermann 2010). The intrinsic value of something is the value that the thing has "in itself," or "as such". In contrast, extrinsic values are derivative values and good for the sake of something else which is intrinsically good. Referring to consent models, the presented values of each model are the pillars the model is built upon. For instance, when the value "autonomy" is undergoing ethical analysis of the values composing autonomy, as e.g. financial independence or freedom of decision-making, (although they might be intrinsic as well) have to be correlated with the covering value (Chang 1997). Eckstein et al. (2014) applies the term "value" to research findings by defining it as a normative property "[…] regarding the worth, significance, or utility of a research finding (whether subjective or objective)". Thus, the finding is necessary for a state of affairs that has worth, significance of utility.

## 5. General argument: constructing the iterative feedback model

The iterative feedback model will be constructed on the basis of the outlined scope of the thesis and the theoretical framework. In chapter four, characteristics of genomic data and an informed consent theory were introduced which will now be applied to the particular case of research using WGS/WES procedures by designing an informed consent model. In several steps that follow in the

next sections ethical principles, positions and informed consent models for research using WGS/WES procedures addressing the disclosure of incidental findings will be carefully weighed, evaluated and incorporated in the design of the iterative feedback model.

## 5.1 Analysis of the iterative feedback model for the return of findings

In order to discuss the obligations of researchers to return findings, it is necessary to clarify the extent of this obligation. In other words, the return of findings is often limited by terms and concepts like "incidental", "analytic validity", "clinical validity", "clinical utility" or "actionability". However, these terms are used in different ways by different authors, and moreover, refer to different cases on which the obligation to return findings is based (Eckstein et al. 2014). Referring to the example by Eckstein et al. (2014) – that a lack of clarity about key terms can sometimes lead to contrary recommendation for the return of findings – it is of great importance to define these terms. Consequently, it should be discussed which findings are mandatory to return from an ethical perspective.

### *5.1.1 Reconstruction of the Presidential Commission's view on returning findings*

The Presidential Commission for the Study of Bioethical Issues report (2013) "Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings" recommends to demarcate four different kinds of findings which do not fall under the term "primary findings" (cf. table 2): "Anticipatable incidental findings" (findings not sought for, but associated with a test or procedure), "unanticipatable incidental findings" (findings not sought for and not anticipated, giving the current state of scientific knowledge which occur due to the vast amount of data potential of WGS/WES), "secondary findings" (findings actively sought for by researchers, but not the primary target) and "discovery findings" (being results of a broad or wide-ranging test that was intended to reveal anything of interest). "Primary findings", in contrast, are the results researchers actively sought for and are associated with the performed procedure (Presidential Commission 2013:28-29).

| TYPE OF RESULT DISCOVERED | DESCRIPTION | EXAMPLE |
|---|---|---|
| **Primary Finding** | Practitioner aims to discover A, and result is relevant to A | In a child with unknown vaccine history, a test done to determine a child's immunity status before the chickenpox vaccine is administered |
| **Incidental Finding:** *Anticipatable* | Practitioner aims to discover A, but learns B, a result known to be associated with the test or procedure at the time it takes place | Discovering misattributed paternity when assessing a living kidney donor and potential recipient who believe they are biologically related[53] |
| **Incidental Finding:** *Unanticipatable* | Practitioner aims to discover A, but learns C, a result not known to be associated with the test or procedure at the time it takes place | When a DTC genetic testing company identifies a health risk based on a newly discovered genetic association not knowable at the time a previous sample was submitted[54] |
| **Secondary Finding** | Practitioner aims to discover A, and also actively seeks D per expert recommendation | ACMG recommends that laboratories conducting large-scale genetic sequencing for any clinical purpose should look for variants underlying 24 phenotypic traits[55] |
| **Discovery Finding** | Practitioner aims to discover A through Z by employing a test or procedure designed to detect a broad array of results | A "wellness scan," a whole body computed tomography (CT) scan, is intended to discover any abnormal finding throughout the body[56] |

Table 2: "Bioethics Commission's Classification of Individualized Results of Medical Tests", Source: Presidential Commission (2013: 27)

Referring to other authors, the Presidential Commission (2013:79) suggests that researchers' ethical obligation to return incidental or secondary findings depends on features of the findings, which are analytical and clinical validity, actionability, clinical or reproductive significance, and the seriousness of potential harm.

The recommendation addressing research findings clearly favours the disclosure of anticipatable incidental findings and deliberately sought secondary findings, as well as the possibility of disclosing unanticipatable incidental findings. The Presidential Commission furthermore highlights that researcher need to respect the wishes of research individuals who want to opt out of receiving incidental findings. However, if researchers express ethical objections to not report such findings (because the information disclosure could be actionable and life-saving), it is recommended not to enrol such individual in research programs (Presidential Commission 2013:87).

A National Institutes of Health Heart, Lung, and Blood working group agreed in 2010 that researchers need to honour participants' expressed preferences. However, they faced the problem of circumstances in which "[...] the evidence of harm is so great, and the potential for reducing the harm too little [...]" (Mountain 2013) and decided to override the participants' wishes on the basis of an IRB decision (Presidential Commission 2013:88). For instance, the discovery of a mutation in the Huntington's gene may be a finding whose evidence of harm is great, but potential treatments to

reduce harm very limited. Moreover, for certain kinds of research, revealing incidental findings is difficult, e.g. for biobank research using de-identified samples. Nevertheless, the Presidential Commission (2013:90) recommends giving "strong reasons" in case of undisclosed findings.

If certain findings are predictably associated with a certain type of research (as it surely is in case of WGS/WES), researchers have the obligation to anticipate such findings to the most possible extent. Subsequently, they are supposed to develop a plan on how to handle anticipatable findings and on how to reveal them to research individuals. Likewise, a plan for unaticipatable incidental findings must be developed (Presidential Commission 2013:89).

### *5.1.2 Reconstruction of Eckstein's et al. view on returning findings*

Eckstein et al. (2014) map out current terminology and concepts for the return of findings by a systematic literature review. The authors standardize "secondary" and "incidental" findings, central terms that they identify, to "secondary findings" following Christenhusz et al. (2013). Eckstein et al. (2014) consider the term "secondary findings" to be of utmost importance because of the relationship between the findings and research. Usually, valid and valuable findings coming directly from research are considered more adequate for disclosure. A common adopted definition of a secondary finding is given by Wolf (2008) (in his paper they use the term "incidental finding"): "a finding concerning an individual research participant that has potential health or reproductive importance and is discovered in the course of conducting research but is beyond the aims of the study. This means that the IFs [incidental findings] may be on variables not directly under study and may not be anticipated in the research protocol."

Eckstein et al. (2014) subsequently highlight the core features of such findings, which are "the relationship of the findings to research", the "relevance/importance of the information to research participants", the "foreseeability" and "the manner in which researchers obtained the findings". Regarding these attributes of secondary findings, those findings must show some potential health or reproductive importance (Wolf 2008) and must furthermore meet the criteria of scientific validity and clinical utility ("relevance of the information"). For instance, if a genetic locus can be associated with a rare disease condition, the finding is directly related to the research aim. The finding is moreover relevant for the participant who consequently knows about the genetic cause of disease. Since the finding is part of the research protocol and it will be actively sought for, it is foreseeable. However, there are findings that are not anticipated in the research protocol (otherwise they would be considered primary research findings). Findings can be results discovered during the

time in which research is ongoing or results discovered by carrying out certain research procedures (Eckstein et al. 2014). Referring to an example of secondary finding, it could turn out that a participant with a rare disease has an elevated risk to develop breast cancer due to a genetic aberration in a known breast cancer gene. In this case, the relationship of the finding to research is not direct, the finding is relevant due to risk and prevention possibilities and the finding is foreseeable because researchers actively seek for it. However, a finding might not be foreseeable if the mutation is located in as yet undiscovered genetic loci for a certain disease condition. In this case, the relevance of a finding is linked to future research revealing new phenotype-genotype relationships.

The second part of Eckstein et al. (2013) presents a new framework for the disclosure of findings and obliterates the distinction between primary and secondary findings. The approach by Eckstein et al. (2013) suggests that certain disclosure requirements distinguish findings that should be disclosed from findings that should be not disclosed. Thus, the authors propose three central concepts that are considered as basis for an obligation to disclose findings: validity, value, and volition. According to the authors, "[...] an obligation to disclose findings exists when findings are valid and have value." Value is defined as "[...] a normative property regarding the worth, significance, or utility of a research finding (whether subjective or objective)". This means that a finding has value if it is significant, utile or worthwhile from the individual perspective or in an objective context (as e.g. in the clinical setting). The third concept addresses an individual's preference, whether he/she is willing to know about the findings or not. Furthermore, the three concepts are only applied to "research findings", meaning that there must be a relationship to research aims and objectives, even if the finding itself is "beyond the aims of the research" or a variant of it (Eckstein et al. 2014). Coming back to the example of the rare diseases genomes project, findings that are not necessarily related to the rare disease are "beyond the aims of the research". Nonetheless, such findings could be the result of specific recommendations, e.g. recommendations given by the ACMG (2013) listing several genes researchers should actively search for. In other words, if researchers investigate certain genes that are stated in the protocol or respectively in the recommendations, they have to go through all genetic abnormalities of these genes. In case an abnormality turns out to be related to a physical condition different from the rare disease, the finding is not directly part of the research aims and objectives, but connected to the procedure. In contrast, mutations which are neither located in the target genes of the protocol nor found in one of the recommended genes would not be considered research findings.

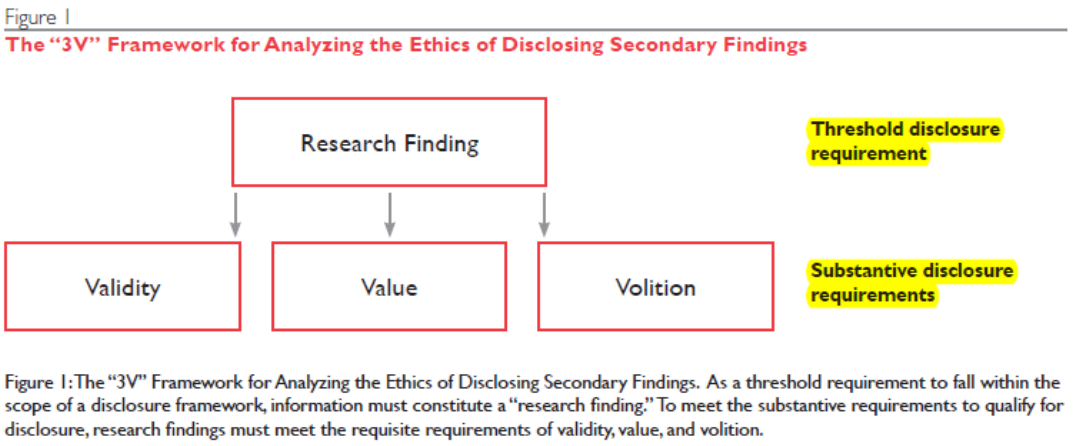



Figure 9: "Framework for Analyzing the Ethics of Disclosing Secondary Findings" by Eckstein et al. (2014)

To tie in with the approach given by Eckstein et al (2014), it is important for the further progress of an informed consent model for research studies using WGS/WES procedures to clearly set the threshold when research findings should be revealed or not. The Presidential Commission (2013) recommends to researchers to develop a clear plan how to manage findings, but misses out to give clear concepts such plans could be based on. As it will be argued in the next section, the iterative feedback model will follow Eckstein et al. (2014), but only partially.

### *5.1.3 The view of the iterative feedback model on returning findings*

In the last two paragraphs I reconstructed the terminology regarding the distinction between several types of research findings given by the Presidential Commission (2013) and Eckstein et al. (2014). Furthermore, I depicted the model for the return of findings presented in the second part of Eckstein's et al. (2014) paper. In this paragraph I show how the iterative feedback model of informed consent critically integrates the analysis of the two major positions available for the ethical obligation of returning findings.

Following the definitions given by the Presidential Commission (2013), the term "incidental findings" will be used in the sense of anticipatable and unanticipatable incidental findings which will be both included in the consent model (cf. Table 3). Furthermore, I follow Eckstein et al. (2014) by not differentiating between secondary findings and incidental findings, as anticipatable incidental and secondary findings are both related to the research project, its procedures, methods and aims ("to find something you must on some level search for it" (Christenhusz et al. 2013)). This means if the researcher anticipates findings in advance of the study conduct, the difference (given by the Presidential Commission (2013)) between "actively seeking for findings" and "certainly discovering findings" leads to the same outcome: findings that are foreseeable or anticipatable

before the research study is conducted. In contrast, unanticipatable incidental findings are not related to the findings researchers primarily seek for. This type of finding are of importance for the iterative feedback model, as it will be also focused on future research discoveries which researchers do not aim for at the very outset of a research study. Unanticipatable incidental findings can occur due to the vast data potential of WGS/WES sequencing technologies. Hence, these findings can be considered a particular characteristic of WGS/WES data and its data heterogeneity.

Incidental findings, including anticipatable and unanticipatable findings, need to meet the standard of analytical validity regarding a certain test procedure to be considered research findings (even though 100% accuracy cannot be reached, cf. chapter two: "Technical validity: specificity and sensitivity of genetic tests"). Furthermore, following Eckstein et al. (2014), findings should be revealed depending on the criterion of volition warranting participants' preferences to know about certain genetic dispositions (MRCT Center Harvard 2015). Also, including the criterion of personal utility, this thesis focuses on the research participants' interest to know about findings which possibly affect health and reproductive decisions. This means that it will not only be focused on findings that are actionable in a narrow sense or fulfill clinical utility. According to Eckstein et al (2014), findings can be valuable even though they might not be valuable in terms of clinical and personal actions. The authors refer to an "indirect non-clinical value" of findings which means that participants may value genetic findings for intrinsic reasons. For instance, a finding could contribute to a "[…] greater understanding of ethnic, cultural and/or personal identity and heritage." (Eckstein et al. 2014). Hence, value as a "[…] normative property regarding the worth, significance, or utility of a finding […]" (Eckstein et al. 2014) must be considered in a certain context. In order to give significance, utility and worth to a finding, the individual background and circumstances of a research participant must be taken into consideration.

To sum up, the iterative model defends that all types of findings that affect health and reproduction, including anticipatable and unanticipatable incidental findings, even though they are not actionable in a narrow sense (e.g. mutations in the Huntington's gene), should be disclosed, as far as the participant is willing to know about them. The threshold set for the disclosure of incidental findings in the thesis framework refers to the "3V" (validity, value and volition) framework by Eckstein et al. (2014). In other words, research findings that are valid, valuable and volitional should be disclosed to research participants.

However, in case of a research participant's preference not to know about actionable and lifesaving findings, I agree with the recommendation by the Presidential Commission (2013) not to enroll such participants in a research study. This is due to the ethical dilemma a researcher faces if he/she is

supposed not to reveal information even though treatment or prevention might be available to improve the participant's outcome.

| | Presidential Commission for the Study of Bioethical Issues (2013) | Eckstein et al. (2014) Fist part | Eckstein et al. (2014) Second part | Holzer (2015) iterative informed consent model |
|---|---|---|---|---|
| **Primary findings** | Findings researchers deliberately seek for | Findings researchers deliberately seek for | The second part of Eckstein et al. (2013) obliterates the distinction between primary and secondary findings of the first part.<br><br>Main classification of findings:<br><br>- Findings that fulfil 3V (should be disclosed)<br><br>- Findings do not fulfil 3V, (should not be discloses)<br><br>the 3V only apply to "research findings", meaning findings related to research aims and objectives, | Findings researchers deliberately seek for |
| **Secondary findings** | Is not focus of research, but researchers actively seek for | Findings with potential health or reproductive importance | | Secondary findings are considered anticipatable incidental findings |
| **Incidental findings *Anti-cipatable*** | Associated with the procedure, but not aim of research | Central terms "secondary" and "incidental" findings are standardized to "secondary findings", following Christenhusz et al. (2013). | | - findings that are not primary aim of research, but known that associated with the test procedure and certainly discovered (anticipated in the research protocol)<br>- recommended to seek for by expert commission (e.g. ACMG)<br>- disclosure if 3V fulfilled |
| **Incidental finding *Unanti-cipatable*** | Result not known to be associated with the test procedure | | | - not anticipated in research protocol<br>- not known to be associated with the test procedure<br>- disclosure if 3V fulfilled |

Table 3: "Comparison of the classification of research findings by the Presidential Commission (2013), Eckstein et al. (2014) and Holzer (2015)"

## 5.2 Ethical principles in the discussion of informed consent models for the return of findings

The management of findings arising in a research context is generally based on the traditional research ethics principles (Presidential Commission 2013:86). As presented in many theoretical frameworks describing and introducing informed consent models, it is necessary to present ethical principles in order to evaluate the presented models (e.g. Appelbaum et al. 2014). A range of ethical principles has been proposed to support informed consent and the return of incidental findings. However, I will present a selection of principles by focusing on those stated by Beauchamp and Childress (2009) and in the Belmont Report (National Commission 1979). These principles will be considered crucial components in the context of WGS/WES data revealing of incidental findings.

Especially in the new field of research on genetic data, it is always dealt with the delicate topic of racism, discrimination, and eugenics that showed us in recent history the possible consequences of missing autonomy. Thus, the stated principles are generally recognized as a minimum demand of the researcher's ethical obligations (Appelbaum et al. 2014:29) to minimize harms history taught us.

With respect to the possible implementation of the suggested iterative feedback model, the four principles "autonomy", "beneficence", "non-maleficence" and "justice" by Beauchamp and Childress are complemented by "practicality" (Appelbaum et al. 2014), a principle that is closely linked to "cost-effectiveness". Furthermore, the principle of "intellectual freedom and responsibility" (Presidental Comission 2013) undergoes ethical analysis.

### *5.2.1 Standard bioethical principles in the discussion of the return of findings*

#### Autonomy

**Autonomy** is usually understood as governance over one's own agency. According to Beauchamp and Childress, "The autonomous individual acts freely in accordance with a self-chosen plan, analogous to the way an independent government manages its territories and establishes its policies" (2009: 99-100). This self-governance is free from controlling interference by others and has to grant adequate understanding, so that meaningful choice is enabled (Beauchamp and Childress 2009). The justification of the autonomy concept grounds in the assumption that self-rule is a central good in our lives (Eyal 2011), promoting our ultimate goals and thus defines how well our lives go (Dworkin 1988). Applied to the discussion of returning findings of WGS/WES procedures used in research settings, the understanding of autonomy as self-governance implies that the "narrow"

understanding, as e.g. the maximization of choice options a participant has by selecting the level of research participation on their own (Kaye et al. 2012 and Hallowell et al. 2014), is rather short-sighted. The "broad" understanding of autonomy is based on an intelligible communicative process that is mandatory to ensure meaningful choices for the individual (Manson and O'Neill 2007, Holzer and Mastroleo 2014). This process necessarily contains information disclosure; full comprehension and voluntariness (cf. NBAC 1995). What we will call the "broad understanding of autonomy" is mostly mentioned in the literature as a major guiding principle named "respect for persons" (National Commission 1979). The principle contains the demand of an autonomous ability to identify personal preferences, act on the own desires, and direct the course of one's life. It can be interpreted as "[…] freedom from limitation that prevent meaningful choice and encompasses dignity and the right to available information even if it does not affect a person's choice" (Presidential Commission 2013).

### Beneficence and non-maleficence

The principles of **beneficence** and **non-maleficence** (Beauchamp and Childress 2009) are crucial principles in research settings. It is necessary to balance possible benefits and risks for an individual participating in research projects. Risk, as I will understand it, is a probability or threat of damage, injury, loss, or any other negative outcome that is caused by an intervention, and that may be not avoided through preventive measures. Risks should never extend possible benefits and harms must be minimized. Since all treatments imply at least a minimal level of risk, it should not be disproportionate to the benefits of a given treatment. It should be emphasized that (ex ante) potential benefits comprise "subjective" or "personal benefits" (cf. "personal utility"), as well as benefits that can be linked to clinical utility. For instance, the discovery of a new gene mutation in rare diseases can be a benefit in itself for the research subject due to the better understanding of disease conditions, but is not necessarily correlated with a better clinical outcome. Furthermore, I want to include the principle of beneficence when it specifically refers to public beneficence supporting society in the pursuit of public benefit, while minimizing personal and public harm (Bioethics Commission 2010). The concept of public benefit includes clinicians, patients, researchers, participants, sponsors and other stakeholders associated with research using WGS/WES procedures.

The Belmont Report states similarly, that the principle of beneficence is required in the research context. Beneficent actions, including non-maleficent actions, are understood in the sense to do no harm and maximize possible benefits and minimize possible harms (National Commission 1979). Furthermore, the Hippocratic maxim "to abstain from doing harm" is considered a crucial principle

and obligation of medical ethics. The obligation of beneficence can be put in the context of particular research projects, as well as in a general context of long term benefits (such as improvement of knowledge and medical treatments) for society (National Commission 1979).

#### Justice

The principle of **justice** (Beauchamp and Childress 2009) addresses the distribution problem of scarce resources in the health sector (Calman 1994). Individuals in similar positions should be treated in a similar way, as public health services show public good characteristics and must be shared equally among all individuals of the community (Goldstein and Pauly 1976). Justice requires that ethically similar cases are treated in a same way. The principle of justice contains furthermore the claim that benefits and burdens of an enterprise are equally distributed among those who might be affected (Presidential Commission 2013). The notion of justice regarding particular informed consent models might change with the progress of time. Access to facilities, as well as to genetic counselling can expand and goes hand in hand with the technological progress (Niedringhaus et al. 2011). In a similar way, the Belmont report formulates that burdens and benefits should be distributed "[…] (1) to each person an equal share, (2) to each person according to individual need, (3) to each person according to individual effort, (4) to each person according to societal contribution, and (5) to each person according to merit" (National Commission 1979).
Furthermore, it is impermissible selecting research subjects due to their class, their availability, their compromised position, or their manipulability.

### *5.2.2 Special principles in the discussion of returning findings*

#### Intellectual freedom and responsibility

The principle of **intellectual freedom and responsibility** (Presidential Commission 2013) supports the intellectual exploration propelling scientific progress. Nonetheless, clinicians, researcher and other agents must take responsibility for their actions, including their intellectual pursuits. Thus, the principle of intellectual freedom and responsibility counters the technological imperative: "The mere fact that something new can be done does not mean it ought to be done" (Presidential Commission 2013:31).

Practicality

The principle of **practicality** (Appelbaum et al. 2014) tries to evaluate if an informed consent model is able to withstand the demands of the model's practical realization (e.g. if the needed facilities are available, as online access, outsourced genetic counseling etc.). First and foremost, practicality seems to be a pragmatic principle focusing on the implementation opportunities of informed consent models. However, it can be argued that practicality can be considered as an ethical principle, as far as the principle of justice comes into play. Under the condition of scarce resources, consent models that are able to grant broader access to health care services for individuals, are more suitable to the principle of justice.

The criterion of **cost-effectiveness** should also be considered in the scope of practicality. Cost effectiveness (Phillips 2009) measures health interventions in a representative monetary value. Its analysis comprises techniques of economic evaluation (NICE 2014). Cost-effective analysis (e.g. cost-utility, cost-benefit analysis) is an economic analysis in which consequences of different interventions are measured using a single outcome (e.g. life years gained, deaths avoided etc.). It is required to choose the optimal intervention regarding the outcome. Society should seek cost-effective ways for health care provision in order to warrant all individuals the access to adequate and affordable services to meet basic health care needs, as demanded by the principle of justice (Presidential Commission 2013:63). Applied to WGS/WES counselling, the gain of counselling and return of incidental findings have to be "weighed" together with the costs that arise in this context. Models showing a high benefit-cost ratio are preferable according to the cost-effective analysis, but cannot be considered independently of other moral considerations.

Depending on the cost effectiveness, the implementation of an informed consent model is sustainable or not which makes it a pragmatic and not an ethical argument. Usually, cost-effective informed consent models are more realizable in a health care system, as costs are low compared to other models of low cost-effectiveness. However, this is not necessarily the case, because cost-effective models could be also costly models with a very favorable outcome showing a high benefit-cost ratio. It is also crucial to mention that the benefit-cost ratio strongly depends on the costs that are included in the cost-benefit analysis and whether costs and benefits for future generations are included. Moreover, it can be difficult to measure benefits and costs especially if they gain in importance in the future. Cost reduction by maintaining the benefits may be reached due to reduced bureaucracy in administration posts, advances in technology and fewer expenses for infrastructure in the public health sector (Enthoven 1988).

## 5.3 The analysis of the iterative model in the light of standard informed consent models for disclosure of incidental findings

When designing an informed consent model, the model should be guided by an informed consent theory. Informed consent models try to apply an ideal consent theory in practical terms by specifying models (cf. Table 4). In the following section, I will introduce four informed consent models for the disclosure of genetic research findings following Appelbaum et al. (2014) who identified prototypic informed consent models based on a literature research. Namely, those models are (1) the traditional informed consent, (2) the staged consent, (3) the mandatory return and (4) the outsourcing informed consent.

The intention is to challenge the models with ethical principles worked out in the previous section, as well as to evaluate their respective advantages principles in a particular context. Importantly, informed consent theories constitute a justification for the particular design of a consent model.
After the evaluation of the models, this section will introduce another informed consent model, the dynamic informed consent, which constitutes in conjunction with the traditional consent model the basis for the iterative feedback model. Differently to the other standard models that will be discussed, the dynamic feedback model has been developed for the research setting of biobanking. Nevertheless, it comprehends a dynamic informed consent process which makes it applicable to the setting of research studies using WGS/WES procedures which are conducted over long time periods and deal with "non-exhaustible" data.
In a next step, I will try to weigh arguments in favor and against these consent models. The last step consists in the development of a new consent model, the iterative feedback model. It will be argued that this model is more appropriate for research studies using WGS/WES procedures and the disclosure of incidental findings.

### Traditional consent model

The (1) traditional consent model favors participants receiving all information about possible incidental findings prior to deciding whether they enroll in a research study. Ideally, a discussion with the participant would cover the characteristics, likelihood and categories of relevant incidental findings, the options for participants for returning some or none of the findings as well as the possible impact on third parties and confidentiality issues. After the discussion, the patient chooses which findings should be revealed and which not (Appelbaum et al. 2014:25).

Stage consent model

In the (2) staged consent, participants receive findings, if there are any, after they occur. Informed consent is obtained in stages, with a short discussion on incidental findings at the beginning, and a more extended consent process if and when reportable results are available (Appelbaum et al. 2014:26).

Mandatory return model

The (3) mandatory return model advocates that participants agree at the beginning of the research project on receiving specific incidental findings that the researcher chooses or that are suggested by certain commissions. For instance, the American College of Medical Genetics and Genomics (ACMG) recommends the disclosure of specific findings related to certain disease categories regardless of the aim of the research study (Green et al. 2013).

Outsourcing model

The (4) outsourcing model suggests to give the participant his/her raw genetic data. Interpretation of data and incidental findings is then provided by an external service (Appelbaum et al. 2014:28).

### *5.3.1 Evaluation of standard informed consent models using ethical principles*

After having shortly depicted these consent models, the next step is to evaluate their ethical validity by applying ethical principles (cf. "Standard bioethical principles in the discussion of returning findings", "Special principles in the discussion of returning findings"), namely "autonomy", "beneficence and non-maleficence", "justice", "intellectual freedom and responsibility", as well as the pragmatic principle of "practicality".

Autonomy

In this paragraph, the core criteria of autonomy, "act on the own considered judgments", "full transmission of relevant information", "full comprehension" and "voluntariness", will be applied to the above described models.
In staged consenting models, participants receive information about incidental findings later, as they arise. This skips the information process prior to research participation. Hence, at the point in time

of decision making whether to participate in a study or not, full comprehension and thus, an autonomous consent cannot be achieved. However, a more detailed information on incidental findings can be discussed at a later point in time (Appelbaum et al. 2014:24) which contributes at least to comprehension in the course of the research study, even though an informed decision for the participation to enroll in the study is still missing.

The mandatory return model leaves the obligation to feedback incidental findings completely in the researcher's hands. Participants agree initially to receive specified incidental findings, transferring the task of decision making to the researcher. Therefore, this model of return of incidental findings does not respect the individual freedom of the participant to act on own considered judgments.

In consent outsourcing models, the raw genetic data material is given to participants who then could make use of second services analyzing the data. Full transmission of relevant information and full comprehension strongly depends on the quality of the external service. Thus, it can be argued that it is part of the researchers' obligation to assure that full comprehension and full transmission of relevant information are granted. Nevertheless, the choice to select findings the participant wants to know about is not rejected.

Finally, the traditional consent model is the only model suggested by Appelbaum et al. (2014) that offers information on incidental findings prior to research participation. Therefore, it can be considered the model which fits best the demanded criteria of full comprehension, full transmission of relevant information and voluntariness in the process of decision making.

### Beneficence and Non-maleficence

Beneficence and non-maleficence are principles that are closely connected to other ethical and pragmatic considerations. Depending on the understanding of benefits and risks, the principles can comprehend personal or public benefits/risks. None of the four models can avoid possible harm to the participants because there will be always the risk that the disclosure of incidental findings causes psychological harm. Especially the staged consent model that does not discuss findings prior to research participation can cause tremendous harm if participants are not prepared to receive the information of incidental findings. In contrast, the traditional model makes the intent to grant minimization of harm due to the option to discuss the findings that are revealed to the participant.

Benefits can be created when findings are disclosed regarding clinical and personal utility and the value of findings. Again, the traditional model can be considered the best attempt to reveal all the findings that could be utile and valuable for the participant, since the participants can utter his/her preferences for particular findings.

The outsourcing model does not necessarily cause harm if the participant does not hire interpreta-

tion services. However, possible benefits would not be disclosed either regarding this scenario.

### Justice

The principle of justice demands that persons in similar cases are treated in a similar way. Furthermore, public health resources should be shared equally among all individuals of the community (Goldstein and Pauly 1976). Regarding the outsourcing model, a problem arises when focusing on the principle of justice. As Appelbaum et al. (2014:29) explain, potentially actionable data that could be disclosed by the researchers is not necessarily accessed due to missing interpretive services. Also, the costs for the disclosure remain outsourced which means that some participants may not be able to afford the services. In this case, participants from lower classes would be systematically excluded from interpretation services. With respect to the traditional model, it can be argued that an intense information process prior to research participation consumes resources that could be invested in other sectors of the health care system. This issue will be addressed in detail in the section on objections to the iterative feedback model and discussed together with the problem of cost-effectiveness.

### Intellectual freedom and responsibility

The principle of intellectual freedom and responsibility supports the intellectual exploration and scientific progress. The second aspect (responsibility) demands researchers to assure that they take on responsibility for their intellectual pursuits. It can be argued that the traditional model hampers medical progress due to a long and complex communication process. Sheehan argues that more standardized consent taking saves resources that could be genuinely spent on the research enterprise (Sheehan 2011). However, even though the outsourcing model avoids in particular the reallocation of resources from the research study to the communication process with the participant, it can be objected that researchers do not assume responsibility to share information with the participants in this model.

### Practicality

The pragmatic principle of practicality is not primary subject to the ethical analysis, but useful to consider with regard to the implementation possibilities of informed consent models. Appelbaum et al. (2014) put emphasis on practicality when evaluating the models (Table 4), as the outlined advantages and disadvantages clearly refer to the practical realization of the models.

First of all, the traditional consent model comprises a long and complex information process which makes the implementation of the model difficult (time and monetary resources have to be available). Additionally, since decision-making is in the participant's hands, there is no exact plan how to deal with preferences of the participant that may change after the initial consent. The staged consent and the mandatory return model comprehend a less time consuming discussion prior to the initial consent. Detailed discussions are linked to concrete findings. Thus, resources are well invested (just spent in case of valuable results for the participant). Also, regarding the mandatory return model, obligations for researchers to feedback findings are clearly defined and can be standardized more easily. Nonetheless, Appelbaum et al. (2014:24) state that re-contacting participants could add to a long and burdensome process, in particular because re-contacting depends on the availability of funding and on a system of communicating with participants. From the researcher's perspective, the outsourcing model might be the most convenient one, since it does not create a burden for researchers to deal with incidental findings. However, the model only works if interpretive genetic services are available in a health care system (Appelbaum et al. 2014:29). In case of the availability of such services and sufficient coverage by a health care insurance, health care resources must be spent for the interpretation of data.

**Table 1.**
**Four Models of Consent to Return of Incidental Findings**

| | *Potential advantages* | *Potential disadvantages* |
|---|---|---|
| **Traditional consent:** Participants receive all information about incidental findings prior to deciding whether to participate. | • The process is familiar to researchers.<br>• Participants maintain choice about receipt of incidental findings. | • Explaining the information adds to an already lengthy and complex process.<br>• Participants' preferences may change after initial consent. |
| **Staged consent:** Participants receive information about incidental findings later, as they arise. | • Less time is spent discussing incidental findings during initial consent.<br>• Participants maintain choice about receipt of incidental findings.<br>• Participants can consider changing circumstances when deciding whether to receive incidental findings.<br>• Participants can receive more detailed and specific information when deciding whether to receive findings. | • Following up and recontacting participants for consent could be costly and burdensome.<br>• Participants decide whether to enroll in study without receiving full information about potential incidental findings.<br>• Depending on the procedure, recontacting the participant can itself reveal unwanted information. |
| **Mandatory return:** Participants agree during initial consent to receive specified incidental findings. | • Consent at enrollment is simpler.<br>• Researchers' obligations to return incidental findings are clearly defined.<br>• Participants maintain choice about whether to participate in the study. | • Participants' choices about receipt of incidental findings are restricted.<br>• Lack of participant choice may be a disincentive to enroll in the research.<br>• Following up and recontacting participants could be costly and burdensome for researchers. |
| **Outsourcing:** Participants receive all raw data and may hire an outside service to interpret data and learn of incidental findings. | • Researchers save time and costs associated with return of incidental findings.<br>• Participant is spared immediate task of deciding which findings to receive.<br>• Researchers' obligations are simplified. | • Interpretive services are not yet widely available.<br>• Interpretive services may be costly and limited to wealthy participants.<br>• Participants who do not hire an interpretive service may not learn of medically significant data. |

Table 4: "Prototypical informed consent models", source: Appelbaum et al. (2014)

### *5.3.2 Dynamic consent model*

After the principle evaluation of standard informed consent models in the previous section, I will introduce a model that serves as a template for the further development of the iterative feedback model for research studies using WGS/WES procedures. Assuming that the participant's autonomy is irrevocable, a consent model called "dynamic consent" has been developed in the context of biobank research which enhances autonomy by offering participants the ability to access their genetic data personally (Steinsbekk et al. 2013). Furthermore, participants can actively participate in the research community of biobanks. Consent taking is a dynamic process, which means that any new research study using the already collected data demands new informed consent taking (Steinsbekk et al. 2013). The Ensuring Consent and Revocation (EnCoRe) project (EnCoRe 2014) has recently demonstrated how this model could be implemented. As part of this project, a web-based platform with an interface allows research participants to have an interactive relationship with

the research community. However, although the interactive communication process optimally transfers benefits to the participants and autonomy is granted via a continuous dialogue within the research community, it can be objected that re-consenting even for minor changes in a research protocols might lead to complications regarding the possibility that research studies are blocked by participants opting out. In this regard, the ethical review of research projects becomes individualized. Control of research projects and responsibilities are shifted from researchers and research ethics committees to participants due to their involvement in research projects (Steinsbekk et al. 2013). On the other hand, this can also be considered as enrichment for the democratic processes in science, ensuring a socially robust knowledge production (Steinsbekk et al. 2013).
Regarding the practicality of the model, problems could arise because online platforms and the facilities to coordinate the participant's involvement have to be available to implement the dynamic consent model. Nevertheless, these possible problems could be solved by future improvements of the health care service.

Drawing a conclusion from the analysis of the discussed informed consent models by applying ethical principles, the most important values and concepts for the design of a consent model should address the minimization of resource consumption, the autonomy of the participant, the prevention of harm, the disclosure of beneficial information, the assumption of responsibility by the research body and equal access to interpretation services.
When designing a consent model for research studies using WGS/WES procedures with the focus on the disclosure of incidental findings, the advantages and disadvantage of the mentioned consent models, as well as the most common values and ethical principles discussed should be taken into account.

### 5.4 The iterative model construction: a first argument in favour of a traditional, non-staged informed consent for research using WGS/WES

As explained in the theoretical groundwork of this thesis, genomic information constitutes a very special type of information (cf. Box 1). Namely, heterogeneity, irreversibility, connectedness to relatives and off-spring and uncertainty underlie the specification and design of an informed consent model. It is important to consider these characteristics accentuating the importance of informed consent taking, which is not trivial. Especially irreversibility and connectedness can have major impacts on an individual's psychological health state.
I will analyze in a first step the specific situation of whole genome data disclosure comprising the crucial characteristics of WGS/WES data in order to weigh advantages and disadvantages of the

introduced consent models more adequately. The further aim of this section is to develop the basis for a model ensuring comprehension and meeting the requirement of autonomy. Autonomy is chosen to be the crucial principle in this context since it is the principle which enhances the participant's empowerment and self-governance. It will be argued using the principle of autonomy that informed consent in the setting of research studies using WGS/WES procedures must aim for a traditional and dynamic consent.

Also, I want to design a consent model putting emphasis on an information process that should be as complete as possible (including full transmission of relevant information and full comprehension which will be explained in more detail) prior to the study enrollment. In consequence, I desist from the staged and mandatory return model because the models lack the transmission of relevant information to grant participant's autonomous choice. In case of the mandatory return model, the participant's option of self-governance is completely undermined. It should also be taken into consideration that findings can reveal irreversible information about very unfavorable health states which moreover impacts on the participant's family, one main reason to involve the participant in the information and decision process.

Mainly, it should be asked, how pros and cons of the introduced consent models are weighed. One way to evaluate this is how different consent models comply with the basics of informed consent requirement as analyzed in section "Informed consent in research using WGS/WES: (1) full transmission of relevant information, (2) comprehension and (3) voluntariness.

### Information transmission

Since information may be very important to the participant's future and even to his family and descendants, it should be assured that the participant is fully aware of these consequences. According to the assumptions regarding the characteristics of WGS/WES data (cf. Box 1: heterogeneity, irreversibility, connectedness, uncertainty), the traditional and dynamic consent seem to be a more appropriate approaches than a staged, mandatory return or outsourcing consent. In other words, delicate and very individual information may ask for a more personal consent process.

### Comprehension

In order to make the revealed information more understandable, a less standardized initial informed consent, as well as a continuous communication process on complex issues addresses better the demand of full comprehension by the participant. Models giving participants full and unlimited

freedom to reign over their data like in the outsourcing model undermine the criterion of comprehension and thus, do not fulfill the requirements of autonomy in its "broad" conception since meaningful choices always depend on a comprehension process where several arguments are critically weighed. The outsourcing model would indeed correspond to the "narrow" understanding of autonomy which refers to the maximization of choice options (Kaye et al. 2012 and Hallowell et al. 2014). However, as argued before, I adopt the "broad" conception of autonomy which is based on an intelligible communicative process that is mandatory to ensure meaningful choices for an individual (Manson and O'Neill 2007, Holzer and Mastroleo 2014).

### Voluntariness

Withdrawing the participant completely from accessing very "personal" (cf. Box 1) information does not meet the demand of autonomy nor the right to profit from possible benefits (Wright et al. 2011). With regard to data heterogeneity, it is difficult from the researchers' perspective to predict firstly, what kind of findings and disease categories should be revealed and secondly, what kind of findings contribute to harm and benefits from the participant's view point. Therefore, it seems to be prudent to involve participants as much as possible in the process of decision making in which he/she has the chance to utter and rethink the own preferences based on the information that is given to him/her, similarly to the dynamic consent.

The only way to respect autonomy of individuals is the implementation of an appropriate informed consent process granting (1) full transmission of relevant information, (2) full comprehension and (3) voluntariness. As I will argue in the next section, this can only be achieved by implementing genetic counselling which I will understand as a personal and individualized communication process. Based on my argumentation, genetic counselling should be a mandatory element prior to research participation using WGS/WES procedures and cannot be skipped. Dealing explicitly with incidental findings, a more profound counselling process might be demanded than in case of counselling on primary findings. Incidental findings –per definition– are not directly related to the research aims and objectives. For instance, if a research project is dedicated to the investigation of candidate genes for rare diseases and the participant has already developed the disease and it turns out that he/she may show an elevated risk to develop a (different) neurological disease in the future, such a finding could have an even greater impact on his/her psychological health.

In conclusion, if we want to implement the principle of autonomy in research using WGS/WES, and given that genetic data exhibits characteristics as heterogeneity, uncertainty, connectedness to third

parties and irreversibility of genetic data – which means that genetic information is individual and delicate for participants – an informed consent model should carefully transmit information in an extended comprehension process prior to the participation in a research study using WGS/WES procedures. In this regard, the iterative feedback model presented in the next step is based on a traditional and dynamic consent and refrains from the staged, mandatory return and outsourcing models.

## 5.5 The iterative feedback model: the final argument

The iterative feedback model is a traditional, non-staged model of informed consent including an extended and most complete counselling process. One of the main ideas of the iterative model is that all relevant information (without mentally overloading individuals) should be transmitted during the informed consent process. By taking up the "dynamic" idea of the dynamic consent model and applying it to the iterative feedback model, the communication process with the participants is not interrupted after the first discussion, implying that changed preferences can be communicated.

The "iterative feedback model" is based on a continuous communication process between counsellor and participant. I define "counsellor" as the person who communicates information and whose task is not necessarily to conduct the research project. However, this will be specified in more detail in the section on "communication process between and counsellor and researcher". Hence, the informed consent process can be considered a holistic or integral process including counselling prior to genomic data collection and counseling on incidental findings after the onset of a research project. I will call the time of information exchange between counsellor and participant "counselling unit". The counsellor is supposedly a geneticist or a qualified physician working at the institution. Every finding related to the research project should be revealed by the counsellor if the participant wants to know about it, as long as the privacy of other research participants is not violated (WHO 2014). Counsellors are supposed to raise awareness of the fact that incidental findings can be discovered in whole genome data analysis. The consent process should furthermore convey "[…] the scope of the findings and to whom the findings will be communicated" (Presidential Commission 2012).

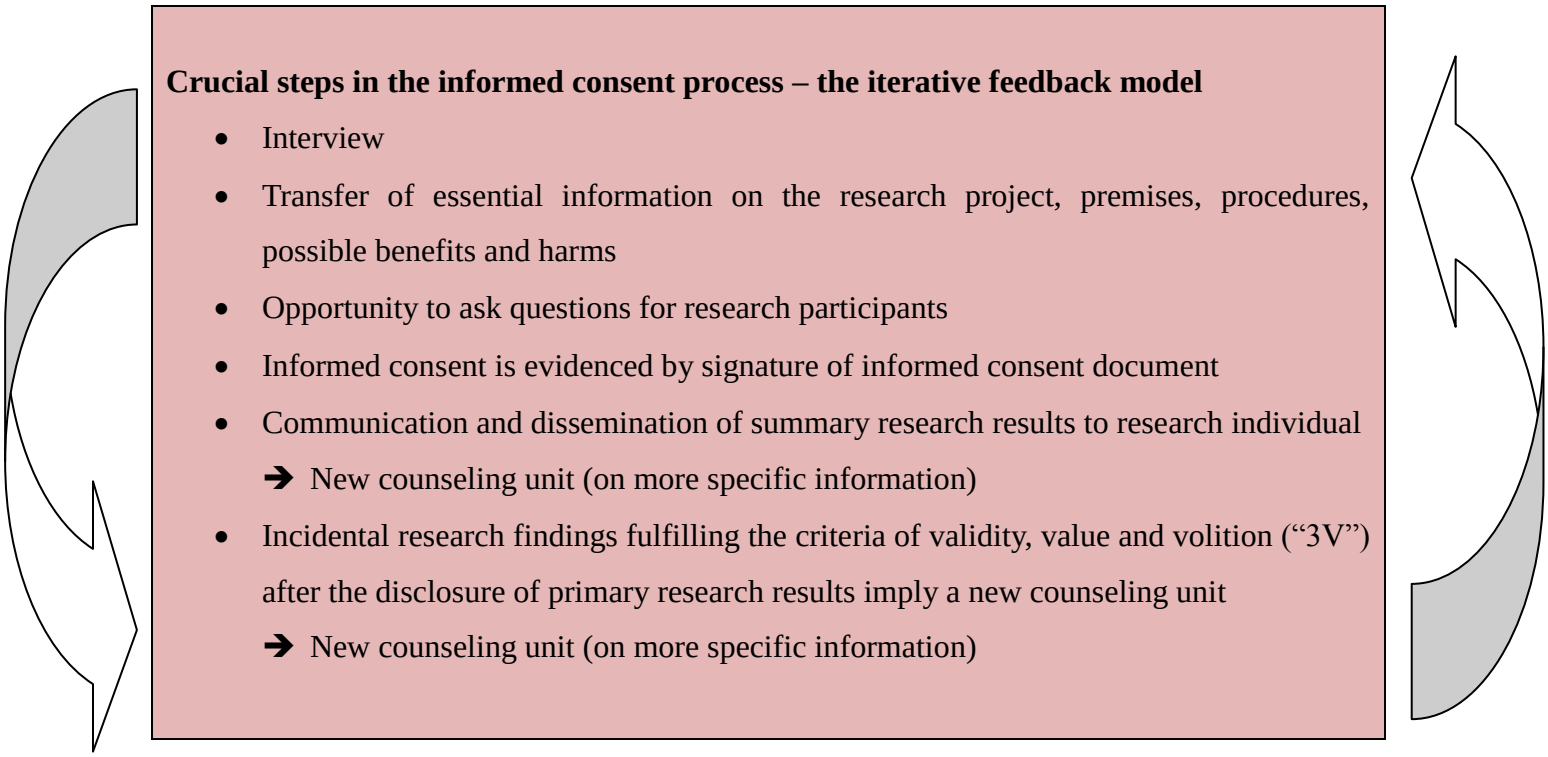
Counselling prior to participation should therefore ensure that the participant understands possible harms and benefits related with data collection and further disclosure. Subsequent counselling units will be necessary as soon as a research finding appears that fulfills the disclosure criteria (c.f. "The view of the iterative feedback model on returning findings") of volition, value and validity. In this

respect, counselling grants full comprehension of possible harms and benefits in every single case of additional valid, valuable and volitional (3V) research findings. This refers also to future unanticipatable incidental findings which can arise e.g. due to improvement in knowledge or changes in recommendation guidelines. Differently to the dynamic model in which participants are enabled to actively participate in a research community via online platforms, personal and continuous ("iterative") counselling is ensured. The dynamic informed consent offers a full involvement in the research project by the suggested online platform where participants stay in touch with the research community, but lacks a structured and guided explanation processes (on incidental findings).

## 6. The iterative feedback model and its implementation into health practice

Box 2 shows crucial steps in the informed consent process of the iterative feedback model. It should be emphasized that the information transfer exhibits an interactive talk between counsellor and participant, supported and underlined by the possibility to ask questions. The whole process needs time to grant full comprehension and a voluntary decision making by the participant. Importantly, full comprehension can be granted after the first counselling unit, but should not be expected in all cases. Comprehension is a function dependent on the variable of time.

**Box 2**




First of all, the counsellor is supposed to discuss the primary findings of a research study the

individual is enrolled in. Once an incidental research finding that fulfills the "3V" framework is at hand, the counsellor should re-contact the participant. It should be mentioned that the "value" that is attributed to a findings strongly depends on the counselling process - the dialogue between counsellor and participant. As mentioned before, value is a normative property regarding significance, worth or utility of a finding (Eckstein et al. 2014) which can be only established in an individual context. Thus, in order to give significance, utility and worth to a finding (Eckstein et al. 2014), the perspectives of counsellor and especially research participant must be taken into account. This can only be achieved by a communicative exchange of different perspectives.

However, the right to refuse to attend a new counselling unit at any point in time must always be given to the participant, as similarly demanded prior to the participation in a research study (World Medical Association 2013, §26). The process of information transmission is taken up again and can be deepened by focusing on new aspects of particular incidental findings. In consequence, the communication of individual results comprehends specific results of the study and incidental findings of the participant (MRCT Center Harvard 2015).

A possible procedure might be that the counsellor initiates a personalized genetic test in order to correctly approve the finding in the participant's personal case. In this way, the counsellor who stays in close contact with the participant is the responsible institution for information disclosure.

## 6.1 Communication process between researcher and counsellor

Firstly, it should be mentioned that counsellor and researcher are not necessarily distinct entities (Hallowell et al. 2014). Since the boundaries between research and genetic counselling nowadays become more and more blurred (Hallowell et al. 2014:2), researcher and counsellor are often the same person.

In order to have a more detailed glance at the counsellor's task, I will introduce the process of information transfer between researchers and counselors which takes place prior to the information disclosure to the participant. As Figure 10 depicts, for the participant relevant data is contained in three types of databases of genetic variants and disease associations that I construct to exemplify relevant data containing individual, public, current and "future" knowledge. Introducing the category data of "future" knowledge, I refer to unanticipatable findings. In the course of scientific advance, there can appear new phenotype-genotype associations which can be of importance for participants whose genomic data have been already sequenced in the past, but which are still

available in databases. Known phenotype-genotype associations as well as new discoveries of such associations are found in the general literature or in public databases (Database 2 and 3). Database 1 contains the data of the particular participant involved in the study. In a first step, the counsellor needs to access the participant's collected data that is held by the researcher (if researcher and counsellor are distinct entities). Furthermore, it has to be checked if there are genetic aberrations of the participant matching common aberrations linked to diseases (database 2). For instance, the current ACMG recommendations (Green et al. 2013) are found in database 2. Hence, it should be sought for mutations in the recommended genes. This is first and foremost the task of research. In an iterative procedure, it has to be screened for newly discovered disease associations either given by database 3 or by the research study itself (database 1). For instance, new publications with respect to primary and incidental findings should be regularly checked and compared to the participant's genome. Importantly, the search for incidental findings should only be initiated if the participant clearly states that he/she wants to know about the type of finding. In case of incidental research findings fulfilling the "3V" framework, a new counselling unit is needed (cf. Box 2). In order to facilitate the counsellor's task, software matching data contained in the three databases would be an essential tool.

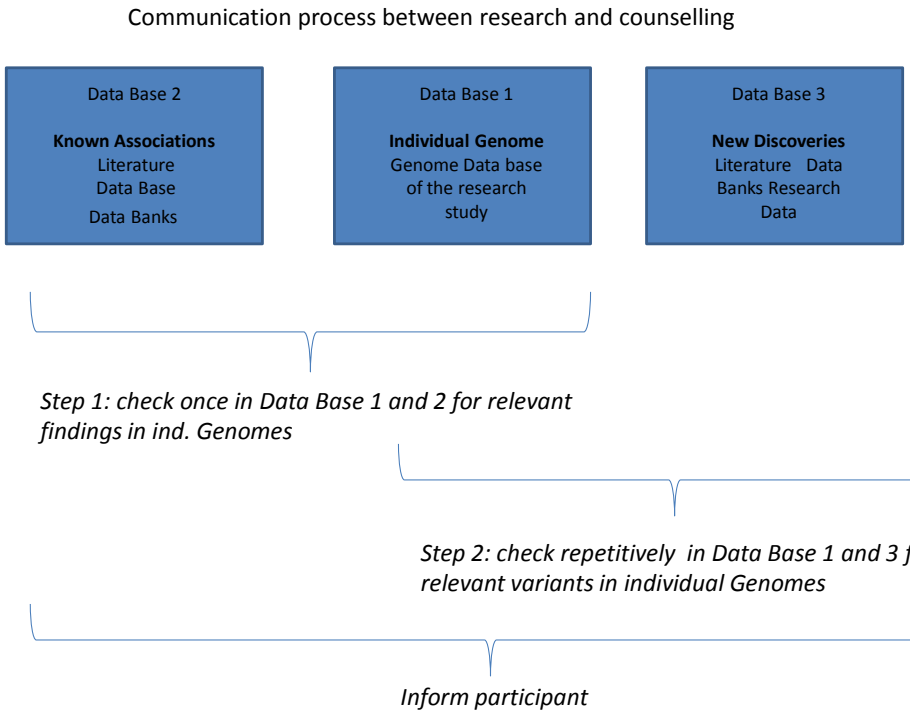



Figure 10: "Communication process between research and counselling after data collection"

## 6.2 Communication process between participants and counsellors

In this paragraph, crucial recommendations in the informed consent process will be outlined by

focusing on the suggestions given by the Presidential Commission (2013: Chapter 3 and 4) on the ethical management of incidental findings in the clinical and research context. The recommendations will subsequently be applied to the case of WGS/WES research and its disclosure of incidental findings.

The informed consent process reveals information on procedures related to the research study, risks, accuracy of the sequencing method (cf. chapter 2), benefits, alternatives and the participant's rights during the procedure. A special emphasis should be put on the characteristics (cf. theoretical framework) of possible WGS/WES finding and the problem of transferring statistical risks to individuals (cf. chapter 2). Also, statements on the purpose of the study and confidentiality are required elements in the informed consent process. The counsellor is supposed to describe findings that are likely to be discovered or findings researchers seek for in the research project. Adequate information comprehends the explanation of crucial characteristics of anticipated incidental findings, as well as the possibility of unanticipated findings that can arise. *Methods of interaction* for the return of findings can comprise face-to-face meetings, telephone calls, two-way online meetings, a dynamic e-mail exchange or other internet based methods. With regard to longitudinal or observational studies (e.g. the rare diseases genomes project), it is recommended to share publications with the research individuals while furthermore supporting their comprehension of research papers via the methods that were explained beforehand (MRCT center at Harvard 2015).

Prior to research enrollment, the counsellor should also convey information about the process for disclosing findings, and explain how participants might opt out of receiving specific findings (Presidential Commission 2013:87). The Presidential Commission (2013:87) states that individuals must not be enrolled in a research study if researchers have ethical objections to allowing participants to opt out whether to receive or not information on findings. For instance, if the researcher considers it unethical not to reveal an important finding that could be of high clinical utility, because a participant opts out this findings prior to research participation, it is legitimate not to enroll the participant in the study (Presidential Commission 2013:87). However, according to the declaration of Helsinki (World Medical Association, §26), the option to opt out of being informed even after the conduct of the research study using WGS/WES procedures, is an essential ethical demand. This could bring researchers and counselors in an ethical dilemma. Comprehensive counselling and a sensitive communication process are the only measures to prevent such a problem.

Anticipated incidental finding (e.g. stated in the ACMG recommendations), i.e. researchers actively search for, must be explicitly mentioned in the first counselling session. For instance, the counsellor

could go through all disease categories of importance with respect to the genes that will be investigated. Moreover, participants should be asked what kind of findings should be revealed to them. Their preferences must always be taken into account and respected (Presidential Commission 2013:64). The categorization of findings likely to be discovered and the sharing of guidelines on this categorization among researchers and counselors could facilitate the information process due to standardized counselling protocols issued in the most complete way.

It could moreover be useful for researcher and participants to develop a plan how to manage intended primary, anticipated as well as unanticipated incidental findings. The search for unanticipatable findings that could be discovered after the onset of a research study due to updates of recommendations or extended genetic knowledge should be discussed with the participant in a separate counselling unit. In this regard, non-clinical researchers could also assess the expertise of clinicians for the discussion with participants, or data from biobanks could support the secondary analysis of findings (Presidential Commission 2013:90).
Moreover, the MRCT Center at Havard (2015) proposes to develop a return of results (ROR) toolkit, including a neutral language guide and a useful checklist, containing the crucial information that must be transferred in counselling units. While a guidance document addresses basic principles, organizational processes, and logistics, the toolkit specifically provides practical examples to sponsors and researchers. Furthermore, the work group suggests a check list addressing crucial questions and information of importance for the research subject.

Recommendations for a "study visit" (counselling session) by the MRCT Center at Harvard (2015):

- Advice regarding monitoring for adverse events, both rare and common, severe and serious, if appropriate
- If questions, or adverse events, whom to contact (and contact information)
- A reminder, if appropriate, that they may be contacted in the future if any adverse events are uncovered that might impact their health.
- Access to any benefits or care as a consequence of participation, if any
- Advice as to where to obtain further treatment and/or clinical care
- Information regarding personal data developed during the study, if appropriate
- Whether they would or would not like to receive summary study results at end of study.
- If opt in to receive RSS, how to access the information and when to anticipate the information. Ensure the format for the data will be accessible
- Contact information for the participant, if appropriate.
- Designation a third party to receive results, if desired

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Table 5: "Recommendation for study visit", Source: MRCT Harvard (2015)

With respect to the required paper work in the informed consent process, it is important to present the information in an understandable way. Factors, a counsellor has to take into account are the age, educational level, the literacy etc. of the potential participant. These tools assure that the content of counselling contains the essential components and respect cultural and literacy conditions of research individuals.

Special attention should be given to health literacy, "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions" (U.S. Department of Health and Human Services (HHS) 2010). Publicly educating participants about primary and incidental findings in research using WGS/WES enables participants to make better informed choices. Especially in low income countries, missing education can lead to a reluctant attitude of participants and non-informed choices (Creed-Kanashiro et al. 2005). For example, materials[2] could be dispersed via channels including mass, digital, and social media. Similarly, the ethical education of researchers and counselors help to communicate research aims, findings etc. in a more thoughtful way.

The education of participants and responsible agents in research and health care should be promoted by federal, state, and local public health institutions (Lachance et al. 2010). Since WGS/WES procedures have the potential to gain more importance in research practice (cf. chapter two, decreasing costs of WGS/WES technologies), educating society about these new technologies could

[2] However, there is not enough evidence that materials facilitate understanding by the research participants. More studies are needed to evaluate what type of material could improve comprehension (Grady 2011).

be facilitated, due to the mere fact that genetic tests become routine practice.

## 6.3 Overview of the communication process

The iterative feedback model offers an approach in which the counsellor bridges the communication process between research subject and researcher (Holzer and Mastroleo 2014). Similarly to the dynamic consent (Figure 11[3]), the participant's preferences and values have to be transmitted to the research team. Research results are disclosed to the participant via the counsellor. Recognizing that much of science happens "bottom-up", resulting in investigations exhibiting scientific value, the iterative model tries to integrate the "top-down" perspective, which means that scientific aspirations honor participants' values and preferences (Might and Miller 2014). The "3V" framework specifically addresses both perspectives (bottom-up and top-down) by setting the standards for the disclosure of incidental findings to validity (in particular important for scientific aspirations), value and volition (which also acknowledge the participant's view point).

If needed, the system gives the opportunity to establish a decentralized genetic counselling process between research institutions and participants, as counselling can be outsourced from research. Nevertheless, the iterative model gives room to variation of the researcher-counsellor relationship. This means that e.g. both tasks can be attributed to the same person. However, in theory, researchers primarily aim to answer research questions, whereas the counsellors should focus on the participant's preferences and values (Hallowell et al. 2014:2). Thus, the tasks of researchers and counselors are clearly separated. Nevertheless, researchers/the principal investigators are the party taking on main responsibility, as they are directly involved in the research study design and the discovery of primary and incidental findings.

[3] Importantly, I do not focus on the data use, but on the occurrence and communication of incidental findings. Figure 11 should give a picture on the information process – however, the content of information is different for the application of the iterative model to the case of research studies using WGS/WES procedures.

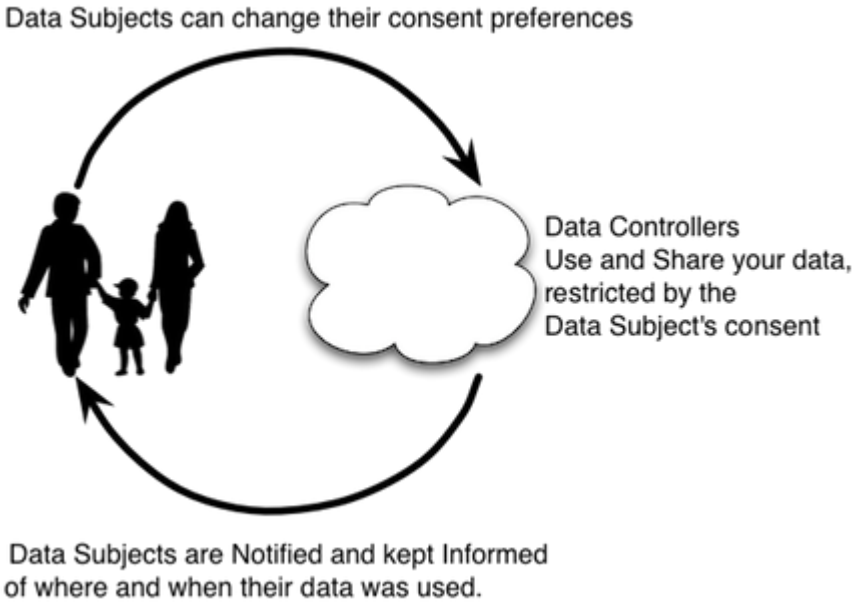


Figure 11: "The dynamic model work flow", Source: Encore project (2012).

### 6.4 The iterative feedback model applied to the case: the rare diseases genomes project revisited

The pillars of the iterative model demand the full disclosure of relevant information, as the background of the research study, possible benefits and risks. The counselor is supposed to explain the dimension of whole genome data. The presented study of the rare diseases genomes project does not only focus on a single preselected gene locus, but investigates a big number of genetic loci and thus, has to be considered in the context of GWAS. Due to the extent of the study, the counsellor has to detail the possibility of incidental findings that can concern different types of phenotypic characteristics. Those characteristics might be of psychological importance, predictive, of high or low risk, concern physical diseases or might affect relatives and offspring. It is important that participants take a voluntary decision whether to participate or not, as soon as they fully understand the given information and know about possible scenarios. The search for certain types of findings is only permitted if the participants clearly express the wish to know about findings. As soon as research results are available, participants have to be informed and new counselling units can be arranged. This leads to an iterative informed consent process based on dialogues, in which participants continuously learn about their genetic data.

## 7. Evaluation of the iterative feedback model

The iterative feedback model meets the principles of autonomy in the sense of self-governance, non-maleficence (because it is a controlled process), beneficence (new findings in research can be

revealed due to the continuous counseling process), and justice (if the access to counselling services does not discriminate on participants' capacity to pay, e.g. if governmental health care systems cover expenses when needed). Furthermore, due to the continuous and ongoing process of understanding, a specific as well as an understandable consent is granted. After having reconstructed the main arguments for the design of the iterative feedback model, I will analyze in the next section the objections that arise when focusing on the practical implementation of the model.

## 7.1 Objections and responses to the iterative informed consent model

Applying informed consent models to a practical setting leads indeed to challenges as far as their implementation is concerned. Thus, it is necessary to discuss the most important objection to the introduction of the iterative feedback model. Four objections will be presented, namely, "resource management", "therapeutic misconception", "post-trial counselling", and "ancillary care obligations". Since the iterative feedback model focuses on an extended communication process between counsellor and participant over long time periods, the objection addressing the resource consumption may be reasonable and very important for the practical implementation. The performance of post-trial counselling also plays a major role in a model advocating continuous counselling. Finally, ancillary care and therapeutic misconception constitute objections that are applicable to informed consent theories and models in a more general way. Nevertheless, these objections are important in the general discussion on informed consent and should be mentioned. In the following paragraphs each objection is introduced and described in the context of the iterative feedback model. Moreover, possible solution that could counter or weaken the discussed problems will be presented as well.

### *7.1.1 Resource management*

It can be objected that the iterative informed consent process is resource consuming and overworks the health system (Hallowell et al. 2014, Sheehan 2011). Therefore, the iterative feedback model potentially faces the problem of cost effectiveness. However, it cannot be assumed without evidence that the iterative informed consent is not cost-effective, as the benefits of the model can possibly exceed the disadvantage of resource consumption. In general, little is known about the cost effectiveness of studies especially in the context of the disclosure of incidental findings (Presidential Commission 2013:67). Considering cost-effectiveness as an outcome that takes into account both the costs and health care benefits of alternative intervention and counselling strategies, it is useful to address the issue of health care cost arising when findings are of clinical relevance (Presidential Commission 2013:67).

Moreover, as the case example of the rare diseases genomes project shows, former health care costs prior to the research project can widely exceed the costs related to the project itself (Perdeaux 2013). Coming back to the case study, two siblings were involved in a diagnostic process for 20 years costing 14,000 pounds (about 21.000 USD) before they participated in the rare diseases genomes project which widely exceeded possible counselling costs linked to the project (Perdeaux 2013). Furthermore, as found in the literature, the perception of cost burden differs enormously among researchers. Some researchers consider costs "too high" and others classify them as "maybe high" (Sofaer et al. 2009). This shows that it might be difficult to define costs.

Furthermore, cost-effectiveness can only be seriously taken into account if the parameters of a particular research study, health care system and counselling mechanism are known. If the prior aim is to protect participants from possible harms and warrant their maximal autonomy in order to support the value of self-governance in our society, the iterative informed consent is able to be cost effective due to the added value it generates, although it remains resource consuming.

Moreover, counselling teams which are personally supervising participants and communicate findings consume fewer resources than the communication process between huge biobanks/research institutions and participants (as suggested by the dynamic model), due to reduced bureaucracy in smaller counselling institutions (Holzer and Mastroleo 2014). In this case, as an alternative to the dynamic consent model, it may not be necessary to provide sophisticated platforms or facilities in order to communicate incidental finding to the participant.
However, information costs due to the communication process between research institutions and counselling services remain. Nonetheless, in university hospitals, where care and research are closely interconnected, the physicians involved in research activities can, after appropriate training, simultaneously perform counselling tasks which could reduce the costs of information transmission between the two branches.

As recommended by the Presidential Commission (2012), the task to support studies to evaluate proposed frameworks for offering return of findings derived from WGS/WES is attributed to funders or sponsors of whole genome sequencing. Funders/sponsors should also support research to investigate preferences, values and expectations of the individuals participating in a research study (Presidential Commission 2012:6-8).
Also, in other settings, counselling services could be provided by Clinical Research Organizations (CROs) if a research study is executed by a CRO. CROs (e.g. TKL research www.tklresearch.com or Accovion www.accovion.com) are third parties that provide allocation services of clinical trials

to big pharmaceutical companies. One work field of CROs (cf. e.g. www.richmondpharacology.com) focuses on "medical writing" which comprises data editing of participants' information, drafts of consent declarations, documentation sheets for the clinical work flow, and adequate publication of collected data and results. This could be extended by counselling services.

As the circumstances require, supportive online services could help the information transmission e.g. by automated messages with short notifications between research and counselling institutions revealing information on new research data. The same automated process could be implemented between counsellor and participant.

### *7.1.2 Therapeutic misconception*

Another more general objection that can be encountered in the literature of research ethics is called therapeutic misconception. With regard to the informed consent process, it is often objected that research participants do not understand the essential distinction between research and care and thus, fail to make meaningful decisions (Henderson et al. 2007:324). In other words, therapeutic misconception is based on the misunderstanding of the difference between the obligations of "researchers to participants" and of "physicians to patients".

In Appelbaum and colleagues' report from interviews with patients with psychiatric disorders (1982), it was shown that research participants were unaware of crucial characteristics of the research study design, such as randomization, non-treatment control groups and placebos or double-blind procedures. The missing capacity of the participants to distinguish between research and treatment marked the term "therapeutic misconception". Henderson et al. (2007) take up this misunderstanding that frequently occurs in research studies, by defining therapeutic misconception as missing understanding "[…] that the defining purpose of clinical research is to produce generalizable knowledge, regardless of whether the subjects enrolled in the trial may potentially benefit from the intervention under study or from other aspects of the clinical trial" (Henderson et al. 2007:1736). This leads to a systematic misunderstanding of the duties that are attributed to researchers (which do not necessarily coincide with the duties of physicians in the context of care). Furthermore, Henderson et al. specify five crucial points that participants should understand in order to not undergo therapeutic misconception (Henderson et al. 2007:1737).

1. It should be understood that the scientific purpose is to generate generalizable knowledge and to answer questions about safety and efficacy of interventions.

2. Participants in trials need to know that research can imply additional study procedures in addition to the intervention.
3. For interventions in the scope of a study, there is often more uncertainty about risks and benefits.
4. Protocols are usually strict on dose, scheduling etc..
5. Clinicians in health care setting provide treatment; in the trial setting they undertake research tasks as investigating safety and efficacy of an intervention.

However, it can be argued against the general objection of therapeutic misconception that firstly, therapeutic misconception strongly depends on the research setting. Appelbaum et al. (1982) could show that therapeutic misconception occurs in the case of patients with psychiatric disorders who are enrolled in a trial using randomization, placebo treatment etc.. In contrast, in the context of research studies using WGS/WES, participants have to be primarily aware of the possible findings that occur in the future. Furthermore, considering GWAS (like e.g. the case study of the rare diseases genomes project) as a subarea of research using WGS/WES procedures, participants are often not involved in conventional study designs with investigative tools, as randomization, placebo treatment etc.. Furthermore, point 2 (additional study procedures to the intervention) and point 4 (strict protocols and schedules) do not necessarily apply to participants of this type of WGS/WES research. However, there might be other settings of research studies using WGS/WES procedures where point 2 and 4 clearly apply.

Secondly, with regard to the other points stated by Henderson et al. (2007), the aim of the iterative feedback model is exactly to prevent the lack of comprehension by

1. an iterative process, facilitating full comprehension of research characteristics due to a temporally extended communication process;
2. a communication procedure in which participants are encouraged to ask questions.

Thirdly, the concept of therapeutic misconception can be criticized in itself. In order to differentiate the obligations of “researchers to participants” and “physicians to patients” (the assumption underlying therapeutic misconception), a difference must exist. It can be contestable whether the obligations of researchers and physicians are clearly different or overlapping.

Tying up to the argument of therapeutic misconception, there is another type of misunderstanding that can be critically discussed. It has to be discussed if “full comprehension” is a feasible aim, even though there is a strong emphasis put on the information transmission in the counselling process of

the iterative feedback model. In the comment "Support for Full disclosure Up Front" (Holzer and Mastroleo 2015), I defended the position to support the information process prior to participation in research studies using WGS/WES procedures which aims for "full comprehension". In the reply to the comment, Appelbaum et al. (2015) argue that "full comprehension" is an elusive endpoint in informed consent to research with regard to increasing amounts of information given to the participants which do not have apparent benefits. Thus, the realization of "full comprehension" might be out of reach. However, as stated in the theoretical framework, "full transmission of relevant information" and "full comprehension" is understood as the individuals' comprehension of relevant information, i.e. what is being asked from them to understand. This systematically excludes an information overload Appelbaum et al. (2015) refer to.

Moreover, Appelbaum et al. (2015) conclude from their assumption (full comprehension as an elusive endpoint) that informed consent cannot and should not necessarily aim for an ideal state of information. The authors mention that none of the discussed models ("Remodeling informed consent models in the context of research using WSG/WES and the disclosure of incidental findings", Appelbaum et al. 2014) achieve the ideal state of information transmission and understanding (Appelbaum et al. 2014) which would justify their eligibility in the ethical debate. Nonetheless, it can be considered an "is-ought" fallacy when saying that the mere fact of an empirical observation (regarding therapeutic misconception) leads to the ethical justification for a model that does not aim for full comprehension. In contrast, the task how to improve the information transmission and the participants' understanding should be subject to the ethical debate when designing an informed consent model.

### *7.1.3 Post-trial counselling*

Since I emphasize in the proposed iterative feedback model a continuous counselling process, problems might arise with respect to counselling obligation years after the research project has been conducted. Here, we encounter a similar problem as post-trial access to beneficial interventions (Mastroleo 2014). Resource consumption over a long time period is one major concern, as well as participant's availability due to address or name changes etc.. In the scope of WGS/WES research and the iterative feedback model, counsellors are supposed to continuously check new research results on genetic aberrations that could be of importance for the patient. Since genetic data is an un-exhaustible pool of data to answer different research questions, post-trial research and information is of high importance. To give a practical example, recommendations like the ACMG guidelines (Green et al. 2013) offering a selection of genes that should be revealed to the participant continuously change due to updates. Thus, post-trial counselling could be necessary for participants,

even a long time after the conduct of a study.
Solving this problem of resource consumption and re-contacting participants may be the practical improvement of the communication process. Software could support counselors by e.g. automatic data matching between data banks and the participant's individual data. Supportive tools should aim for a reduction of time and resource consuming procedures.

### *7.1.4 Ancillary care obligations*

Another problem arising in the context of a WGS/WES studies concerns ancillary care obligations. Ancillary care is defined as health care that participants need which is not necessarily connected to safety or scientific validity of the research, injuries caused by the research study or to the fulfillment of moral demands promised in the informed consent process (Richardson and Belsky 2004:26). Especially in developing countries, ancillary care is of main importance due to the limited access to health care resources (Merritt 2011). In this work, there is no such focus on obligations because they are beyond the return of incidental findings and related to health care. If findings are revealed in the informed consent process, they can be of importance for the diagnosis of a disease. Therapeutic consequences, if there are treatment options or preventive measures, would have to be considered apart from the research study.
However, the question that arises is very important in the WGS/WES research context and addresses further moral obligations of researchers and counsellors to provide adequate care for clinically significant findings that remain unrelated to the primary research question. In the context of WGS/WES research, such findings could be primary or incidental. Thus, there is need of a normative model addressing the question how to deal with ancillary care. Specifically, it should be answered (1) if there are ancillary care obligations (referring to a basis of principles) and (2) if yes, for which type of findings they are mandatory (content of moral obligations). (3) The lower and upper limits of the extension of the obligation should be non-arbitrarily located (cf. Merritt 2011).
Furthermore, Merritt (2011) offers an interesting approach to show moral obligations of ancillary care, based on the general obligations (duties of justice and rescue) and special obligations (grounded in the researcher-participant relationship, including the concept of trust etc.). Applied to the case of WGS/WES research, it can be argued there are obligations to provide health care in case of findings that reveal genetic aberrations that are connected to clinically significant results that can potentially be treated. These obligations also have to involve the health care providers covering treatments or prevention.

## Chapter 5. General conclusion

In the course of this thesis, I have evaluated different informed consent models and their implementation into clinical practice which was guided by ethical principles and the reflection on specific characteristics of WGS/WES data. Drawing a conclusion from the analysis of the discussed informed consent models, there are important principles, values and concepts underlying these models, like cost-effectiveness, guaranty of autonomy, comprehension, and protection of participants/minimization of harms. The advantages and disadvantage of the consent models, as well as the most common values and ethical principles have been taken into account.
This evaluation built the basis for the rationale to develop a new informed consent model in the context of research studies involving human subjects and using WGS/WES procedures, the iterative feedback model. I tried to design a model that is able to apply to the specific characteristics of WGS/WES by incorporating the ethical principles stated in the framework. However, there are still objections to the implementation of the iterative feedback model like in particular the problem of resource consumption. Nevertheless, the model offers many advantages, especially with regard to the approach to the informed consent requirement, namely voluntariness, full transmission of relevant information and full comprehension.

In more detail, I justify a consent model for counselling prior to research participation and for the return of incidental findings after the onset of the research study. The communication between researchers and participants is linked by the counsellor (who explains the research study and reveals findings) and is embedded in a continuous counselling process. Furthermore, I have shown how the model could be implemented into practice on the basis of the current “rare diseases genomes project” in the United Kingdom.

## Summary

After having outlined in Chapters 2 and 3 the biological and technical background of WGS/WES technologies, the technical characteristics of WGS/WES test procedures, the historical review of informed consent and its legal implementation, the general aim of the thesis consisted in the development of an informed consent model for the disclosure of incidental findings in the setting of clinical research studies involving human participants and using WGS/WES procedures.
The scientific Chapter 2 and the historical and political perspective of Chapter 3 provided the background for a better understanding of ethical issues concerning the informed consent requirement adapted to WGS/WES technologies. Subsequently, Chapter 4 reconstructed the ethical

arguments for the design of the "iterative feedback model" which has been supported by the case of the "rare diseases genomes project", a genome wide association study. Two strategies were applied to prove the hypothesis that the iterative feedback model fits best the ethical demands of consent taking for the disclosure of incidental findings in research studies using WGS/WES. On the one hand, the most important characteristics of WGS/WES data, namely heterogeneity, irreversibility, connectedness, and uncertainty were outlined and it has been discussed why an informed consent model must comprise a comprehensive and continuous (iterative) communication process to match these characteristics. On the other hand, an ethical framework for consent taking has been developed addressing ethical and pragmatic principles that are commonly found in the literature for informed consent. As an intermediate step, I analyzed and challenged common informed consent models for the disclosure of incidental findings in genomic research (Appelbaum et al. 2014) based on ethical principles. Subsequently, advantages and disadvantages of the models resulting from this evaluation have been outlined. The iterative feedback model was developed to avoid (most of the) disadvantages with a special focus on the evaluation of the principle of "autonomy" which should be granted by the newly introduced model. In consequence, both strategies led us to the iterative feedback model, a model based on a traditional consent (communication prior to research participation) and on a dynamic consent (communication over time, involvement of the participant). Thus, the iterative model takes up the basic idea of the traditional and dynamic consent to communicate with the participants and to involve them actively and continuously in a communication process. However, differently to the dynamic consent, the iterative model offers a guided process of understanding to approach the complex issues arising in the context of research using WGS/WES procedures. While participants of the dynamic model communicate with researchers via an online platform, the iterative feedback model offers a specific and individual communication process assuring that all relevant information is communicated.

Secondly, the aim has been to describe the iterative feedback model in more detail. "Counselling" was introduced as continuous communication process between counsellor and participant. The counsellor has been described as the link between researcher and participant, comparable to a personal mentor who goes through possible risks, benefits and outcomes of the research study and counsels on incidental findings that occur during the research conduct. Following Eckstein et al. (2014), a section was dedicated to elaborate the criteria, namely validity, value and volition (the "3V" framework) a research findings must meet in order to be revealed to the participant. Also important to mention is that the participant's autonomously chosen preferences should be taken into consideration when seeking for and revealing incidental findings. This means that both, researcher and counselor are ethically required to respect participants and to respond to their questions,

concerns and wishes. Hence, the counselling process is supposed to contribute to the participant's autonomy and to come up to the informed consent requirement comprising voluntariness, full transmission of relevant information and full understanding.

Thirdly, possible objections to the iterative feedback model were stated addressing "resource management", "therapeutic misconception", "post-trial counselling" and "ancillary care obligations". Regarding the first objection, resource management, I tried to outline that it may be difficult to estimate costs for the implementation of the iterative feedback model due to the different parameters that vary among all types of research studies using WGS/WES. Secondly, even if the implementation of the model is linked to high expenses, cost-effectiveness could be still granted through the superior benefits of the model (higher expenses are compensated by higher benefits). Also, it has been argued that supportive infrastructure for counselling services, as well as the financial contribution of research funders and sponsors could reduce the costs for the health care system.

Furthermore, Appelbaum et al. (2015) states that participants are not able to understand relevant information for a fully autonomous choice. Responding to this objection, I argued that the iterative feedback model is an attempt to facilitate the understanding of participants. With regard to therapeutic misconception, this argument applies as well. When participants get confused with the distinction between the obligations of "researchers to participants" and of "physicians to patients" (assuming there are distinct obligations), an extended communication process is the only way to prevent such misunderstanding.

## Outlook and further research

This dissertation provides an initial approach to the informed consent requirement in the particular setting of human health research studies using WGS/WES technologies. Not all aspects and challenges could be addressed in this thesis (cf. "Scope of the thesis"). The iterative feedback model implies post-trial counselling obligations over years. One major concern might be that re-contacting participants years after a study is conducted could add to a long and difficult process. However, online platforms could facilitate to stay in touch with the participants. Furthermore, it has been beyond the thesis' aims to discuss ancillary care obligation in case of clinically actionable findings. Nevertheless, this is an important field in which research should be done. I considered it an ethical debate in itself to discuss the obligations of counsellors and researchers to provide adequate care for clinically significant findings that remain unrelated to the primary research question. Also, if there

is an obligation to provide care, it should be discussed which findings come into consideration for ancillary care obligations.

Other topics that could not be addressed in the dissertation were “obligations towards third parties”, “confidentiality issues” and “storing, sharing and distribution of genomic data”. Hence, there are many important ethical issues related to new sequencing technologies and procedures that arise within each of the mentioned work fields.

Moreover, it should be considered in future studies, how and which supportive tools, as software for data evaluation, online platforms or toolkits (e.g. the MRCT toolkit for the return of research results), could be helpful for the cost-effective implementation of the iterative feedback model. This is of importance in order to ensure a continuous counselling process over long time periods which should not excessively consume resources. Also, it would be helpful to do a systematic literature research on informed consent forms and the proposed recommendations on essential content and process in WGS/WES research which could be applied to the standards of counselling. Likewise, there has been work done for WGS studies in the clinical setting, extrapolating the most essential information that should be included in informed consent (Ayuso et al. 2013).

In future work, there is still need to focus on the practical implementation of the iterative feedback model. The dissertation offers the theoretical and ethical framework for the informed consent model. Nevertheless, it would be of help to focus on empirical qualitative data to support the hypothesis that research using WGS/WES procedures needs an extended and iterative counselling process. Also, to address the objection of resource consumption, it could be focused on a very specific setting, respectively on a particular research study using WGS/WES procedures, to evaluate expenses and benefits resulting from the application of the iterative feedback model.

In spite of the exploratory nature of this thesis, I have introduced the iterative feedback model with the firm aim to contribute tackling the ethical aspects of the fast development of new sequencing technologies which are rapidly becoming routine technologies. Especially when considering the tendency of the cost-reduction potential of sequencing technologies, WGS/WES tends to become an established practice in research and clinical care. In this regard, the model adapts the informed consent requirement to the technological trend. As history shows, the adaption and development of the informed consent requirement has been always linked to the misuse of participants or new technological and medical procedures. In the same way, the thesis adapts the informed consent process to the characteristics of WGS/WES in order to keep pace with the application possibilities

of WGS/WES.

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